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(54) Title: NEW EFFECTOR CONJUGATES, PROCESS FOR THEIR PRODUCTION AND THEIR PHARMACEUTICAL USE

(57) Abstract: Conjugates of epothilones and epothilone derivatives (as effectors) with suitable biomolecules (as recognition units) are described. Their production is carried out by the effectors being reacted with suitable linkers, and the compounds that are produced are conjugated to the recognition units. The pharmaceutical use of the conjugates for treating proliferative or angiogenesis-associated processes is described.

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New Effector Conjugates, Process for their Production and their Pharmaceutical Use

The development of the understanding relating to the recognition of binding regions, especially in the field of monoclonal antibodies or fragments thereof against specific tumor antigens, makes it possible to consider a selective tumor therapy by specific release of an anti-tumor active agent at the target site.

A precondition for such an approach, in which a highly active (toxic) active agent (effector) is coupled to a high-molecular, tumor-specific recognition unit, such as, for example, to an antibody, is a substantial inactivity of the conjugate, whose minimum components are represented by a recognition unit and an effector, until it has reached the target site (tumor). Arriving at the target site, the conjugate binds to the cell surface and the active ingredient, optionally after the preceding internalization of the entire complex, can be released.

The successful therapy of solid tumors, especially with monoclonal antibodies, can be limited, however, by an inadequate penetration of the antibody into the tumor as well as the heterogeneous dispersion of the corresponding tumor-associated antigens in the tumor tissue.

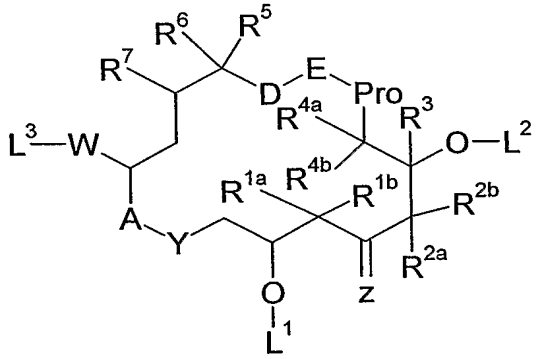
These limitations could be avoided in that the tumor-vascular system is attacked in a specific way. The growth of tumors below a volume of about 2 mm^3 depends on a neoangiogenesis. The subsequent tumor growth is based on an intact vascular system, which ensures the supply with nutrients or the removal of waste products. The selective destruction of this system should therefore result in a necrosis of the tumor. The attack on the vascular system of the tumor promises a number of advantages relative to the direct attack on the tumor itself. In comparison to tumor cells, endothelial cells are easier to access, since no tumor tissue has to be penetrated. The damage of an individual tumor vessel should result in a necrosis of thousands of tumor cells. To damage a tumor vessel, it is not necessary to kill all endothelial cells. The specific attack of endothelial cells in or close to the tumors minimizes systemic side effects. Endothelial cells are genetically very stable, so that the probability of a development of resistance against the tumor therapeutic agent is low.

Within the scope of this invention, surprisingly enough, a possibility has now been found to link the chemically very sensitive, highly-functionalized class of active agents of epothilones and analogs thereof to a high-molecular recognition unit via different linkers in different positions of the active agent.

The object of this invention is thus, *inter alia*,

1. to find a method to link highly active active agents from the structural class of the epothilones and epothilone derivatives to suitable linkers,
2. to synthesize suitable linkers,
3. to develop a method to link these epothilone-linker conjugates to recognition units, such as, for example, monoclonal antibodies or fragments thereof, to form immune conjugates that are both chemically and metabolically sufficiently stable for the development of a pharmaceutical, and that are superior to the epothilones or epothilone derivatives that are taken as a basis with respect to their therapeutic range, their selectivity of action and/or undesirable toxic side effects and/or the degree of their activity.

This invention accordingly comprises effector conjugates of general formula I



I,

in which

R^{1a}, R^{1b}, independently of one another, are hydrogen, C_1-C_{10} alkyl, aryl, aralkyl,

or together a $-(CH_2)_m$ group, in which m is 2 to 5,

R^{2a}, R^{2b}, independently of one another, are hydrogen, C_1-C_{10} alkyl, aryl, aralkyl, or together a $-(CH_2)_n$ group, in which n is 2 to 5, or C_2-C_{10}

alkenyl, or C_2-C_{10} alkynyl,

R^3 is hydrogen, C_1-C_{10} alkyl, aryl or aralkyl, and

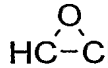
R^{4a}, R^{4b}, independently of one another, are hydrogen, C_1-C_{10} alkyl, aryl, aralkyl, or together a $-(CH_2)_p$ group, in which p is 2 to 5,

R^5 is hydrogen, C_1-C_{10} alkyl, aryl, aralkyl, CO_2H, CO_2alkyl, CH_2OH, CH_2OAlkyl, CH_2OAcyl, CN, CH_2NH_2, CH_2N(alkyl, acyl)$_{1,2}$, or CH_2Hal,

Hal is a halogen atom,

R^6, R^7 in each case are hydrogen, or together an additional bond, or together an oxygen atom, or together an NH group, or together an N-alkyl group, or together a CH_2 group, and

G is an oxygen atom or CH_2,

D-E is a group H_2C-CH_2, HC=CH, C≡C, CH(OH)-CH(OH), CH(OH)-CH_2, CH_2-CH(OH),  , O-CH_2, or, if G represents a CH_2 group, D-E is CH_2-O,

W is a group C(=X)R^8, or a bi- or tricyclic aromatic or heteroaromatic radical,

L^3 is hydrogen, or, if a radical in W contains a hydroxyl group, forms a group

O-L^4 with the latter, or, if a radical in W contains an amino group, forms a

group NR^{25}-L^4 with the latter,

R^{25} is hydrogen or C_1-C_{10} alkyl,

X is an oxygen atom, or two OR^{20} groups, or a C_2-C_{10} alkylenedioxy group

that may be straight-chain or branched, or H/OR^9, or a $CR^{10}R^{11}$ group,

R^8 is hydrogen, C_1-C_{10} alkyl, aryl, aralkyl, halogen or CN, and

R^9 is hydrogen or a protective group PG^X,

R^{10}, R^{11} in each case independently of one another, are hydrogen, C_1-C_{20} alkyl,

aryl, aralkyl, or together with a methylene carbon atom form a 5- to 7-membered carbocyclic ring,

Z can represent oxygen or H/OR^{12},

R^{12} can represent hydrogen or a protective group PG^Z,

A-Y can represent a group O-C(=O), O-CH_2, CH_2-C(=O), NR^{21}-C(=O) or NR^{21}-SO_2,

R^{20} can represent C_1-C_{20} alkyl,

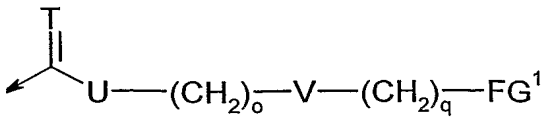
R^{21} can represent a hydrogen atom or C_1-C_{10} alkyl,

PG^X, PG^Y, and PG^Z can represent a protective group PG, and

L^1, L^2, and L^4, independently of one another, can represent hydrogen, a group C(=O)Cl, a group C(=S)Cl, a group PG^Y or a linker of general formula (III) or (IV);

provided that at least one substituent L^1, L^2 or L^4 represents a linker of general formula (III) or (IV);

the linker of general formula (III) has the following structure,



III,

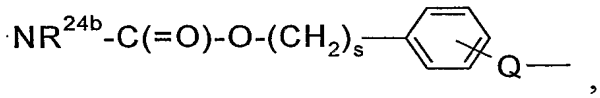
in which

T can represent oxygen or sulfur,

U can represent oxygen, CHR^{22}, CHR^{22}-NR^{23}-C(=O)-, CHR^{22}-NR^{23}-C(=S)-, O-C(=O)-CHR^{22}-NR^{23}-C(=O)-, O-C(=O)-CHR^{22}-NR^{23}-C(=S)- or NR^{24a},

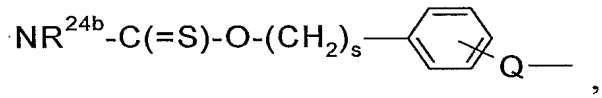
o can represent 0 to 15,

V can represent a bond, aryl, a group



,

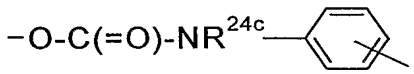
or a group



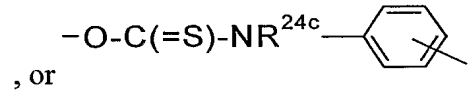
,

s can represent 0 to 4,

Q can represent a bond, O-C(=O)-NR^{24c}, O-C(=S)-NR^{24c},



, or



R^{22} can represent hydrogen, C_1-C_{10} alkyl, aryl or aralkyl,

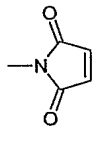
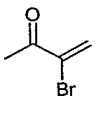
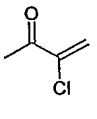
R^{23} can represent hydrogen or C_1-C_{10} alkyl,

R^{24a}, R^{24b}, and R^{24c}, independently of one another, can represent hydrogen

or

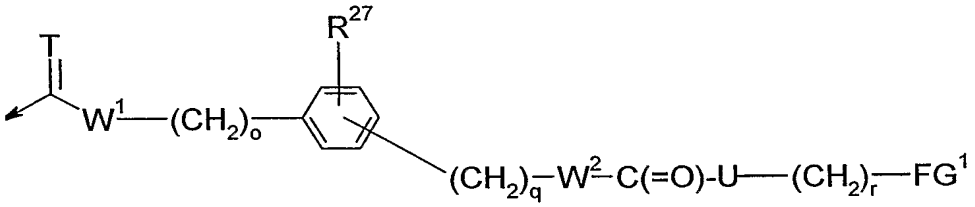
C_1-C_{10} alkyl,

q can represent 0 to 15,

FG^1 can represent C_1-C_{10} alkyl-S_3,  ,  ,  ,  ,

 , or CO_2H; and

the linker of general formula (IV) has the following structure,



IV,

in which

T can represent oxygen or sulfur,

W^1, W^2 are the same or different and can represent oxygen or NR^{24a},

o can represent 0 to 5,

R^{22} can represent hydrogen, C_1-C_{10} alkyl, aryl or aralkyl,

R^{23} can represent hydrogen, or C_1-C_{10} alkyl,

R^{24a} can represent hydrogen or C_1-C_{10} alkyl,

R^{27} can represent halogen, CN, NO_2, CO_2R^{28}, or OR^{28},

R^{28} can represent hydrogen, C_1-C_{10} alkyl, aryl or aralkyl,

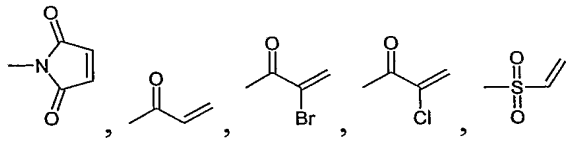
q can represent 0 to 5,

U can represent oxygen, CHR^{22}, CHR^{22}-NR^{23}-C(=O)-, CHR^{22}-NR^{23}-C(=S)-

or C_1-C_{20} alkyl,

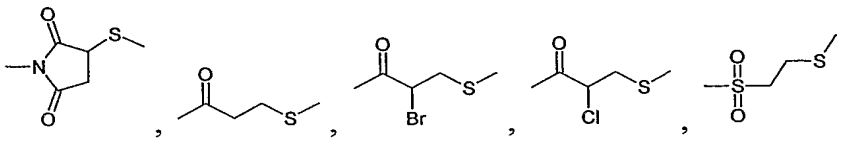
r can represent 0 to 20,

FG^1 can represent C_1-C_{10} alkyl-S_3,



as a single isomer or a mixture of different isomers and/or as a pharmaceutically acceptable salt thereof.

In addition, the invention describes the production of effector recognition unit conjugates of general formula (I), wherein the substituents therein have the above-mentioned meanings, but at least one group FG^1 is replaced by a group FG^{2a} or FG^{2b}, wherein FG^{2a} or FG^{2b} can have the following meanings:

FG^{2a}: -S-S-, 

FG^{2b}: -CONH-

and wherein a recognition unit is conjugated via a sulfur atom with the group FG^{2a}, wherein the indicated sulfur atom is a component of the recognition unit, or via an amide function of group FG^{2b}, wherein the indicated nitrogen atom is a component of the recognition unit;

wherein the recognition unit can be, for example, a peptide, a soluble receptor, a cytokine, a lymphokine, an aptamer, a spiegelmer, a recombinant protein, a framework structure, a monoclonal antibody or a fragment of a monoclonal antibody.

According to this invention, the above-mentioned effector recognition unit conjugates can comprise one or more recognition units; in this case, the recognition units that belong to a conjugate can be identical or different. It is preferred that the recognition units of a conjugate be identical.

The effector recognition unit conjugates according to the invention can be used in the form of their α-, β- or γ-cyclodextrin-clathrates or in the form of liposomal or pegylated compositions.

The conjugates according to the invention are preferably used for the treatment of diseases that are associated with proliferative processes. For example, the therapy of different tumors, the therapy of inflammatory and/or neurodegenerative diseases, such as multiple sclerosis or Alzheimer's disease, the therapy of angiogenesis-

associated diseases such as the growth of solid tumors, rheumatoid arthritis or diseases of the ocular fundus, can be mentioned.

The production of epothilones, their precursors and derivatives of general formula I is carried out according to the methods that are known to one skilled in the art, as they are described in, for example, DE 19907588, WO 98/25929, WO 99/58534, WO 99/2514, WO 99/67252, WO 99/67253, WO 99/7692, EP 99/4915, WO 00/485, WO 00/1333, WO 00/66589, WO 00/49019, WO 00/49020, WO 00/49021, WO 00/71521, WO 00/37473, WO 00/57874, WO 01/92255, WO 01/81342, WO 01/73103, WO 01/64650, WO 01/70716, US 6204388, US 6387927, US 6380394, US 02/52028, US 02/58286, US 02/62030, WO 02/32844, WO 02/30356, WO 02/32844, WO 02/14323, and WO 02/8440.

As alkyl groups R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^3, R^{4a}, R^{4b}, R^5, R^8, R^{10}, R^{11}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24a}, R^{24b}, R^{24c}, R^{25} and R^{26}, straight-chain or branched-chain alkyl groups with 1-20 carbon atoms can be considered, such as, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert.-butyl, pentyl, isopentyl, neopentyl, heptyl, hexyl, and decyl.

Alkyl groups R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^3, R^{4a}, R^{4b}, R^5, R^8, R^{10}, R^{11}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24a}, R^{24b}, R^{24c}, R^{25} and R^{26} can also be perfluorinated or substituted by 1-5 halogen atoms, hydroxy groups, C_1-C_4-alkoxy groups or C_6-C_{12}-aryl groups (which can be substituted by 1-3 halogen atoms).

As aryl radicals R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^3, R^{4a}, R^{4b}, R^5, R^8, R^{10}, R^{11}, R^{22}, R^{26} and V, substituted and unsubstituted carbocyclic or heterocyclic radicals with one or more heteroatoms, such as phenyl, naphthyl, furyl, thienyl, pyridyl, pyrazolyl, pyrimidinyl, oxazolyl, pyridazinyl, pyrazinyl, quinolyl, thiazolyl, benzothiazolyl or benzoxazolyl, which can be substituted in one or more places by halogen, OH, O-alkyl, CO_2H, CO_2-alkyl, $-NH_2$, $-NO_2$, $-N_3$, -CN, C_1-C_{20}-alkyl, C_1-C_{20}-acyl or C_1-C_{20}-acyloxy groups, are suitable. The heteroatoms can be oxidized provided that this does not cause the aromatic character to be lost, such as, for example, the oxidation of a pyridyl to a pyridyl-N-oxide.

As bicyclic and tricyclic aryl radicals W, substituted and unsubstituted, carbocyclic or heterocyclic radicals with one or more heteroatoms such as naphthyl, anthryl, benzothiazolyl, benzoxazolyl, benzimidazolyl, quinolyl, isoquinolyl, benzoxazinyl, benzofuranyl, indolyl, indazolyl, quinoxalinyl, tetrahydroisoquinolinyl,

tetrahydroquinolinyl, thienopyridinyl, pyridopyridinyl, benzopyrazolyl, benzotriazolyl, or dihydroindolyl, which can be substituted in one or more places by halogen, OH, O-alkyl, CO_2H, CO_2-alkyl, $-NH_2$, $-NO_2$, $-N_3$, -CN, C_1-C_{20}-alkyl, C_1-C_{20}-acyl or C_1-C_{20}-acyloxy groups, are suitable. The heteroatoms can be oxidized provided that this does not cause the aromatic character to be lost, such as, for example, the oxidation of a quinolyl to a quinolyl-N-oxide.

The aralkyl groups in R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^3, R^{4a}, R^{4b}, R^5, R^8, R^{10}, R^{11}, R^{22} and R^{26} can contain in the ring up to 14 C atoms, preferably 6 to 10 C atoms, and in the alkyl chain 1 to 8 atoms, preferably 1 to 4 atoms. As an aralkyl radical, for example, benzyl, phenylethyl, naphthylmethyl, naphthylethyl, furylmethyl, thienylethyl or pyridylpropyl is suitable. The rings can be substituted in one or more places by halogen, OH, O-alkyl, CO_2H, CO_2-alkyl, $-NO_2$, $-N_3$, -CN, C_1-C_{20}-alkyl, C_1-C_{20}-acyl or C_1-C_{20}-acyloxy groups.

As representatives of protective groups PG, tris(C_1-C_{20} alkyl)silyl, bis(C_1-C_{20} alkyl)-arylsilyl, (C_1-C_{20} alkyl)-diarylsilyl, tris(aralkyl)-silyl, C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_4-C_7-cycloalkyl, which in addition can contain an oxygen atom in the ring, aryl, C_7-C_{20}-aralkyl, C_1-C_{20}-acyl, aroyl, C_1-C_{20}-alkoxycarbonyl, C_1-C_{20}-alkylsulfonyl as well as arylsulfonyl can be cited.

As alkyl-, silyl- and acyl radicals for the protective groups PG, especially the radicals that are known to one skilled in the art are considered. Preferred are the alkyl or silyl radicals that can be easily cleaved from the corresponding alkyl and silyl ethers, such as, for example, the methoxymethyl, methoxyethyl, ethoxyethyl, tetrahydropyranyl, tetrahydrofuranyl, trimethylsilyl, triethylsilyl, tert.-butyldimethylsilyl, tert.-butyldiphenylsilyl, tribenzylsilyl, triisopropylsilyl, benzyl, para-nitrobenzyl, and para-methoxybenzyl radicals, as well as alkylsulfonyl and arylsulfonyl radicals. As an alkoxycarbonyl radical, e.g., trichloroethyloxycarbonyl (Troc) is suitable. As an acyl radical, e.g., formyl, acetyl, propionyl, isopropionyl, trichloromethylcarbonyl, pivalyl, butyryl or benzoyl, which radical can be substituted with an amino and/or hydroxy group, is suitable.

As amino protective groups PG, the radicals that are known to one skilled in the art are suitable. For example, the Alloc, Boc, Z, benzyl, f-Moc, Troc, stabase or benzostabase group can be mentioned.

As halogen atoms, fluorine, chlorine, bromine or iodine can be considered.

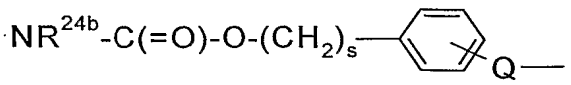
The acyl groups can contain 1 to 20 carbon atoms, formyl, acetyl, propionyl, isopropionyl and pivalyl groups being preferred.

The C_2-C_{10}-alkylene-α,ω-dioxy group that is possible for X is preferably an ethylene ketal or neopentyl ketal group.

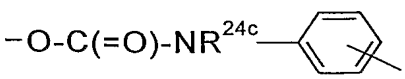
Preferred compounds of general formula I are those in which A-Y represents O-C(=O) or NR^{21}-C(=O); D-E represents an H_2C-CH_2 group; G represents a CH_2 group; Z represents an oxygen atom; R^{1a}, R^{1b} in each case represent C_1-C_{10} alkyl or together a $-(CH_2)_p$ group with p equal to 2 or 3 or 4; R^{2a}, R^{2b}, independently of one another, represent hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, or C_2-C_{10} alkynyl; R^3 represents hydrogen; R^{4a}, R^{4b}, independently of one another, represent hydrogen or C_1-C_{10} alkyl; R^5 represents hydrogen, or C_1-C_4 alkyl or CH_2OH or CH_2NH_2 or $CH_2N(alkyl, acyl)_{1,2}$ or CH_2Hal; R^6 and R^7 together represent an additional bond or together an NH group or together an N-alkyl group or together a CH_2 group or together an oxygen atom; W represents a group $C(=X)R^8$ or a 2-methylbenzothiazol-5-yl radical or a 2-methylbenzoxazol-5-yl radical or a quinolin-7-yl radical or a 2-aminomethylbenzothiazol-5-yl radical or a 2-hydroxymethylbenzothiazol-5-yl radical or a 2-aminomethylbenzoxazol-5-yl radical or a 2-hydroxymethylbenzoxazol-5-yl radical; X represents a $CR^{10}R^{11}$ group; R^8 represents hydrogen or C_1-C_4 alkyl or a fluorine atom or a chlorine atom or a bromine atom; R^{10}/R^{11} represent hydrogen/2-methylthiazol-4-yl or hydrogen/2-pyridyl or hydrogen/2-methyloxazol-4-yl or hydrogen/2-aminomethylthiazol-4-yl or hydrogen/2-aminomethyloxazol-4-yl or hydrogen/2-hydroxymethylthiazol-4-yl or hydrogen/2-hydroxymethyloxazol-4-yl.

As linkers of general formula (III), compounds are preferred in which V represents a bond or an aryl radical, o is equal to zero, and T represents an oxygen atom.

As linkers of general formula (III), in addition compounds are preferred in which V represents a bond or an aryl radical or a group

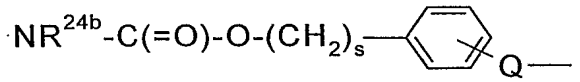


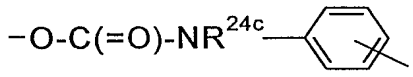
; Q represents a bond or a group



; and o is 0 to 4. Especially preferred are compounds

of general formula (III), wherein V represents a bond or a group


; Q represents a bond or a group


; o is equal to 0, 2 or 3; s is equal to 1; and T is an oxygen atom.

As linkers of general formula (IV), compounds are preferred in which o is zero to four, and q is zero to three. Especially preferred are compounds of general formula (IV), wherein o is 0, 2 or 3; W^1 is an oxygen atom; q is equal to 0; R^{22} is hydrogen, C_1 –C_3 alkyl or aralkyl; R^{23} is hydrogen or C_1 –C_3 alkyl; R^{24a} is hydrogen or C_1 –C_3 alkyl; R^{27} is fluorine, chlorine, CN, NO_2, CO_2R^{28} or OR^{28}; R^{28} is hydrogen or C_1 –C_5 alkyl; and U is oxygen, CHR^{22} or CHR^{22}–NR^{23}–C(=O)-.

As recombinant proteins for use as recognition units, for example, binding regions derived from antibodies, so-called CDRs, are suitable.

As framework structures for use as recognition units, for example, high-molecular structures that are not derived from antibodies are suitable. For example, structures of the fibronectin type 3 and of crystallins can be mentioned.

As fragments of monoclonal antibodies for use as recognition units, for example, single-chain Fv, Fab, $F(ab)_2$ as well as recombinant multimers can be mentioned.

As preferred recognition units, those are considered that are suitable for, for example, the recognition and/or diagnosis and/or therapy of solid tumors and malignant diseases of the hematopoietic system.

As recognition units that are additionally preferred, those are considered that allow a selective recognition of the disease-specific vascular system, preferably of the angiogenesis.

Table 1 cites examples of especially preferred recognition units for treating solid tumors.

TABLE 1

Tumor	Antigen Identity/ Characteristics	Monoclonal Antibodies	References
Gynecol. (GY)	CA 125' > 200 kD mucin GP	OC 125	Kabawat et al., 1983; Szymendera, 1986
Ovarian	80 Kd GP	OC 133	Masuko et al., Cancer Res, 1984
Ovarian	'SGA' 360 Kd GP	OMI	de Krester et al., 1986
Ovarian	High M_r mucin	Mo v1	Miotti et al., Cancer Res, 1985
Ovarian	High M_r mucin/ glycolipid	Mo v2	Miotti et al., Cancer Res, 1985
Ovarian	NS	3C2	Tsuji et al., Cancer Res, 1985
Ovarian	NS	4C7	Tsuji et al., Cancer Res, 1985
Ovarian	High M_r mucin	ID3	Gangopadhyay et al., 1985
Ovarian	High M_r mucin	DU-PAN-2	Lan et al., 1985
GY	7700 Kd GP	F 36/22	Croghan et al., 1984
Ovarian	'gp 68' 48 Kd GP	$4F_7/7A_{10}$	Bhattacharya et al., 1984
GY	40, 42kD GP	OV-TL3	Poels et al., 1986
GY	'TAG-72' High M_r mucin	B72.3	Thor et al., 1986

Tumor	Antigen Identity/ Characteristics	Monoclonal Antibodies	References
Ovarian	300-400 Kd GP	DF_3	Kufe et al., 1984
Ovarian	60 Kd GP	$2C_8/2F_7$	Bhattacharya et al., 1985
GY	105 Kd GP	MF 116	Mattes et al., 1984
Ovarian	38-40 kD GP	Mov18	Miotti et al., 1987
GY	'CEA' 180 Kd GP	CEA 11-H5	Wagener et al., 1984
Ovarian	CA 19-9 or GICA	CA 19-9 (1116NS 19-9)	Atkinson et al., 1982
Ovarian	'FLAP' 67 Kd GP	H17-E2	McDicken et al., 1985
Ovarian	72 Kd	791T/36	Perkins et al., 1985
Ovarian	69 Kd PLAP	$NDOG_2$	Sunderland et al., 1984
Ovarian	unknown M_r PLAP	H317	Johnson et al., 1981
Ovarian	$p185^{HER2}$	4D5, 3H4, 7C2, 6E9, 2C4, 7F3, 2H11, 3E8, 5B8, 7D3, SB8	Shepard et al., 1991
Uterus, Ovary	HMFG-2	HMFG2	Epenetos et al., 1982
GY	HMFG-2	3.14.A3	Burchell et al., 1983
Breast	330-450 Kd GP	DF3	Hayes et al., 1985
Breast	NS	NCRC-11	Ellis et al., 1984
Breast	37kD	3C6F9	Mandeville et al., 1987
Breast	NS	MBE6	Teramoto et al., 1982
Breast	NS	CLNH5	Glassy et al., 1983

Tumor	Antigen Identity/ Characteristics	Monoclonal Antibodies	References
Breast	47 Kd GP	MAC 40/43	Kjeldsen et al., 1986
Breast	High M_r GP	EMA	Sloane et al., 1981
Breast	High M_r GP	HMFG1 HFMG2	Arklie et al., 1981
Breast	NS	3.15.C3	Arklie et al., 1981
Breast	NS	M3, M8, M24	Foster et al., 1982
Breast	1 (Ma) Blood Group Ags	M18	Foster et al., 1984
Breast	NS	67-D-11	Rasmussen et al., 1982
Breast	Estrogen Receptor	D547Sp, D75P3, H222	Kinsel et al., 1989
Breast	EGF Receptor	Anti EGF	Sainsbury et al., 1985
Breast	Laminine Receptor	LR-3	Horan Hand et al., 1985
Breast	*erb* B-2 p185	TA1	Gusterson et al., 1988
Breast	NS	H59	Hendler et al., 1981
Breast	126 Kd GP	10-3D-2	Soule et al., 1983
Breast	NS	HmAB1,2	Imam et al., 1984; Schlom et al., 1985
Breast	NS	MBR 1,2,3	Menard et al., 1983
Breast	95 Kd	24-17-1	Thompson et al., 1983
Breast	100 Kd	24-17-2 (3E1-2)	Croghan et al., 1983
Breast	NS	F36/22.M7/105	Croghan et al., 1984
Breast	24 Kd	C11, G3, H7	Adams et al., 1983

Tumor	Antigen Identity/ Characteristics	Monoclonal Antibodies	References
Breast	90 Kd GP	B6-2	Colcher et al., 1981
Breast	CEA & 180 Kd GP	B1-1	Colcher et al., 1983
Breast	Colon & pancreas, mucin-like Ca 19-9	Cam 17-1	Imperial Cancer Research Technology MAb listing
Breast	Milk mucin, nuclear protein	SM3	Imperial Cancer Research Technology Mab listing
Breast	Milk mucin, nuclear protein	SM4	Imperial Cancer Research Technology Mab listing
Breast	Affinity-purified milk mucin	C-Mul (566)	Imperial Cancer Research Technology Mab listing
Breast	$P185^{HER2}$	4D5 3H4, 7C2, 6E9, 2C4, 7F3, 2H11, 3E8, 5B8, 7D3, 5B8	Shepard et al., 1991
Breast	CA 125 > 200 Kd GP	OC 125	Kabawat et al., 1985
Breast	High M_r mucin/ glycolipid	MO v2	Miotti et al., 1985
Breast	High M_r mucin	DU-PAN-2	Lan et al., 1984

Tumor	Antigen Identity/ Characteristics	Monoclonal Antibodies	References
Breast	'gp48' 48 Kd GP	$4F_7/7A_{10}$	Bhattacharya et al., 1984
Breast	300-400 Kd GP	DF_3	Kufe et al., 1984
Breast	'TAG-72' high M_r mucin	B72-3	Thor et al., 1986
Breast	'CEA' 180 Kd GP	ccccCEA 11	Wagener et al., 1984
Breast	'PLAP' 67 Kd GP	H17-E2	McDicken et al., 1985
Breast	HMFG-2 > 400 Kd GP	3-14-A3	Burchell et al., 1983
Breast	NS	FO23C5	Riva et al., 1988
Colorectal	TAG-72 High M_r mucin	B72-3	Colcher et al., 1987
Colorectal	GP37	(17-1A) 1038-17-1A	Paul et al., 1986
Colorectal	Surface GP	CO17-1A	LoBuglio et al., 1988
Colorectal	CEA	ZCE-025	Patt et al., 1988
Colorectal	CEA	AB2	Griffin et al., 1988a
Colorectal	Cell surface AG	HT-29-15	Cohn et al., 1987
Colorectal	Secretory epithelium	250-30.6	Leydem et al., 1986
Colorectal	Surface glycoprotein	44X14	Gallagher et al., 1986
Colorectal	NS	A7	Takahashi et al., 1988
Colorectal	NS	GA73-3	Munz et al., 1986
Colorectal	NS	791T/36	Farrans et al., 1982

Tumor	Antigen Identity/ Characteristics	Monoclonal Antibodies	References
Colorectal	Cell Membrane & Cytoplasmatic Ag	28A32	Smith et al., 1987
Colorectal	CEA & Vindesin	28.19.8	Corvalen, 1987
Colorectal	gp72	X MMCO-791	Byers et al., 1987
Colorectal	high M_r mucin	DU-PAN-2	Lan et al., 1985
Colorectal	high M_r mucin	ID_3	Gangopadhyay et al., 1985
Colorectal	CEA 180 Kd GP	CEA 11-H5	Wagener et al., 1984
Colorectal	60 Kd GP	$2C_8/2F_7$	Bhattacharya et al., 1985
Colorectal	CA-19-9 (or GICA)	CA-19-9 (1116NS 19-9)	Atkinson et al., 1982
Colorectal	Lewis a	PR5C5	Imperial Cancer Research Technology Mab Listing
Colorectal	Lewis a	PR4D2	Imperial Cancer Research Technology Mab Listing
Colorectal	Colon mucus	PR4D1	Imperial Cancer Research Technology Mab Listing
Melanoma	$P97^a$	4-1	Woodbury et al., 1980
Melanoma	$P97^a$	8-2 M_{17}	Brown, et al., 1981a

Tumor	Antigen Identity/ Characteristics	Monoclonal Antibodies	References
Melanoma	$P97^b$	96-5	Brown, et al., 1981a
Melanoma	$P97^c$	118-1, 133-2, (113-2)	Brown, et al., 1981a
Melanoma	$P97^c$	L_1, L_{10}, R_{10} (R_{19})	Brown et al., 1981b
Melanoma	$P97^d$	I_{12}	Brown et al., 1981b
Melanoma	$P97^e$	K_5	Brown et al., 1981b
Melanoma	P155	6-1	Loop et al., 1981
Melanoma	G_{D3} disialogan-gliosides	R24	Dippold et al., 1980
Melanoma	P210, p60, p250	5-1	Loop et al., 1981
Melanoma	P280 p440	225.28S	Wilson et al., 1981
Melanoma	GP 94, 75, 70 & 25	465.12S	Wilson et al., 1981
Melanoma	P240-P250, P450	9-2-27	Reisfeld et al., 1982
Melanoma	100, 77, 75 Kd	F11	Chee et al., 1982
Melanoma	94 Kd	376.96S	Imai et al., 1982
Melanoma	4 GP Chains	465.12S	Imai et al., 1982; Wilson et al., 1981
Melanoma	GP 74	15-75	Johnson & Reithmuller, 1982
Melanoma	GP 49	15-95	Johnson & Reithmuller, 1982

Tumor	Antigen Identity/ Characteristics	Monoclonal Antibodies	References
Melanoma	230 Kd	Mel-14	Carrel et al., 1982
Melanoma	92 Kd	Mel-12	Carrel et al., 1982
Melanoma	70 Kd	Me3-TB7	Carrel et al., 1:387, 1982
Melanoma	HMW MAA similar to 9-2-27 AG	225.28SD	Kantor et al., 1982
Melanoma	HMW MAA similar to 9-2-27 AG	763.24TS	Kantor et al., 1982
Melanoma	GP95 similar to 376-96S 465-12S	705F6	Stuhlmiller et al., 1982
Melanoma	GP125	436910	Saxton et al., 1982
Melanoma	CD41	M148	Imperial Cancer Research Technology Mab listing
Gastrointestinal (GI)	high M_r mucin	ID3	Gangopadhyay et al., 1985
Gallbladder, Pancreas, Stomach	high M_r mucin	DU-PAN-2	Lan et al., 1985
Pancreas	NS	OV-TL3	Poels et al., 1984
Pancreas, Stomach, Esophagus	'TAG-72' high M_r mucin	B72-3	Thor et al., 1986

Tumor	Antigen Identity/ Characteristics	Monoclonal Antibodies	References
Stomach	'CEA' 180 Kd GP	CEA 11-H5	Wagener et al., 1984
Pancreas	HMFG-2 > 400 Kd GP	3-14-A3	Burchell et al., 1983
GI	NS	C COLI	Lemkin et al., 1984
Pancreas, Stomach	CA 19-9 (or GICA)	CA-19-9 (1116NS 19-9) and CA50	Szymendera, 1986
Pancreas	CA125 GP	OC125	Szymendera, 1986
Lung	$p185^{HER2}$	4D5, 3H4, 7C2, 6E9, 2C4, 7F3, 2H11, 3E8, 5B8, 7D3, SB8	Shepard et al., 1991
Non-small-cell lung cancer (NSCLC)			
NSCLC	high M_r mucin/glycolipid	MO v2	Miotti et al., 1985
NSCLC	'TAG -72' high M_r mucin	B72-3	Thor et al., 1986
NSCLC	High M_r mucin	DU-PAN-2	Lan et al., 1985
NSCLC	'CEA' 180 kD GP	CEA 11-H5	Wagener et al., 1984
Malignant Glioma	Cytoplastic antigen that consists of 85HG-22 cells	MUG 8-22	Stavrou, 1990

Tumor	Antigen Identity/ Characteristics	Monoclonal Antibodies	References
Malignant Glioma	Cell surface Ag that consists of 85HG-\63 cells	MUC 2-63	Stavrou, 1990
Malignant Glioma	Cell surface Ag that consists of 86HG-39 cells	MUC 2-39	Stavrou, 1990
Malignant Glioma	Cell surface Ag that consists of 86HG-39 cells	MUG 7-39	Stavrou, 1990
Gl, Other	P53	PAb 240, PAb 246, PAb 1801	Imperial Cancer Research Technology MaB Listing
Small, Round-Cell Tumors	Neural cell adhesion molecules	ERIC-1	Imperial Cancer Research Technology MaB Listing
Medulloblas-tomas, Neuro-blastomas, Rhabdomyo-sarcomas		M148	Imperial Cancer Research Technology MaB Listing

Tumor	Antigen Identity/ Characteristics	Monoclonal Antibodies	References
Neuro-blastomas		FMH25	Imperial Cancer Research Technology MaB Listing
Kidneys & Glioblastomas	P155	6-1	Loop et al., 1981
Bladders & Laryngeal Tumors	"Ca Antigen" 350-390 kD	CA1	Ashall et al., 1982
Neuroblastoma	GD2	3F8	Cheung et al., 1986
Prostate	Gp48 48 kD GP	$4F_7/7A_{10}$	Bhattacharya et al., 1984
Prostate	60 kD GP	$2C_8/2F_7$	Bhattacharya et al., 1985
Thyroid	'CEA' 180 kD GP	CEA 11-H5	Wagener et al., 1984
Prostata	Neurocellin-2 (NC-2), TMEFF2, TENB2, tomoregulin, TMP-2	2H8, 10G6	Berlex

As especially preferred recognition units for treating hematological tumors, antibodies or antibody fragments, such as CD19, CD20, CD40, CD22, CD25, CD5, CD52, CD10, CD2, CD7, CD33, CD38, CD40, CD72, CD4, CD21, CD5, CD37 and CD30, can also be mentioned.

As especially preferred recognition units for anti-angiogenic therapy, antibodies or fragments thereof, such as VCAM, CD31, ELAM, endoglin, VEGFRI/II, $\alpha_v\beta_3$, Tie1/2, TES23 (CD44ex6), phosphatidylserine, PSMA, VEGFR/VEGF complex or ED-B-fibronectin, can be mentioned.

The compounds that are mentioned below are especially preferred according to the invention as effector elements:

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-1-methyl-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S(E))-16-[2-(2-Aminomethyl-thiazol-4-yl)-1-methyl-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-1-methyl-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S(E),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-1-methyl-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-methyl-2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-1-methyl-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S(E))-16-[2-(2-Aminomethyl-thiazol-4-yl)-1-methyl-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-methyl-2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-1-methyl-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]hepta-decane-5,9-dione,

(1S,3S(E),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-1-methyl-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]hepta-decane-5,9-dione,

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-fluoro-2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-1-fluoro-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-thiazol-4-yl)-1-fluoro-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-fluoro-2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-1-fluoro-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-1-fluoro-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-chloro-2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-1-chloro-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-thiazol-4-yl)-1-chloro-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-chloro-2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-1-chloro-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-1-chloro-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-fluoro-2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-1-fluoro-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-thiazol-4-yl)-1-fluoro-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-fluoro-2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-1-fluoro-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]hepta-decane-5,9-dione,

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-1-fluoro-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]hepta-decane-5,9-dione,

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-chloro-2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-1-chloro-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-thiazol-4-yl)-1-chloro-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-chloro-2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-1-chloro-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]hepta-decane-5,9-dione,

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-1-chloro-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]hepta-decane-5,9-dione,

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-methyl-2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-methyl-2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-fluoro-2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-fluoro-2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-chloro-2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-chloro-2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-fluoro-2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-fluoro-2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-chloro-2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-chloro-2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl-oxazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-oxazol-4-yl)-1-methyl-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S(E))-16-[2-(2-Aminomethyl-oxazol-4-yl)-1-methyl-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-oxazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-oxazol-4-yl)-1-methyl-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S(E),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-oxazol-4-yl)-1-methyl-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-methyl-2-(2-methyl-oxazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-oxazol-4-yl)-1-methyl-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S(E))-16-[2-(2-Aminomethyl-oxazol-4-yl)-1-methyl-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-methyl-2-(2-methyl-oxazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-oxazol-4-yl)-1-methyl-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]hepta-decane-5,9-dione,

(1S,3S(E),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-oxazol-4-yl)-1-methyl-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]hepta-decane-5,9-dione,

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-fluoro-2-(2-methyl-oxazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-oxazol-4-yl)-1-fluoro-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-oxazol-4-yl)-1-fluoro-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-fluoro-2-(2-methyl-oxazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-oxazol-4-yl)-1-fluoro-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-oxazol-4-yl)-1-fluoro-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-chloro-2-(2-methyl-oxazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-oxazol-4-yl)-1-chloro-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-oxazol-4-yl)-1-chloro-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-chloro-2-(2-methyl-oxazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-oxazol-4-yl)-1-chloro-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-oxazol-4-yl)-1-chloro-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-fluoro-2-(2-methyl-oxazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-oxazol-4-yl)-1-fluoro-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-oxazol-4-yl)-1-fluoro-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-fluoro-2-(2-methyl-oxazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-oxazol-4-yl)-1-fluoro-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]hepta-decane-5,9-dione,

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-oxazol-4-yl)-1-fluoro-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]hepta-decane-5,9-dione,

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-chloro-2-(2-methyl-oxazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-oxazol-4-yl)-1-chloro-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-oxazol-4-yl)-1-chloro-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-chloro-2-(2-methyl-oxazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-oxazol-4-yl)-1-chloro-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]hepta-decane-5,9-dione,

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-oxazol-4-yl)-1-chloro-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]hepta-decane-5,9-dione,

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S(E))-16-[2-(2-Aminomethyl-thiazol-4-yl)-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S(E),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S(E))-16-[2-(2-Aminomethyl-thiazol-4-yl)-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S(E),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-propyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-propyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-propyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-propyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-propyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-propyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-butyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-butyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-butyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-butyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-butyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-butyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-allyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-allyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-allyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-allyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-allyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-allyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-prop-2-inyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-prop-2-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-prop-2-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-prop-2-inyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-prop-2-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-prop-2-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-but-3-enyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-but-3-enyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-but-3-enyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-but-3-enyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-but-3-enyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-but-3-enyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-but-3-inyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-but-3-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-but-3-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-but-3-inyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-but-3-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-but-3-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-propyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-propyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-propyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-propyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-propyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-propyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-butyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-butyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-butyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-butyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-butyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-butyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-allyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-allyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-allyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-allyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-allyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-allyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-prop-2-inyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-prop-2-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-prop-2-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-prop-2-inyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-prop-2-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-prop-2-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-but-3-enyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-but-3-enyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-but-3-enyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-but-3-enyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-but-3-enyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-but-3-enyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-but-3-inyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-but-3-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-but-3-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

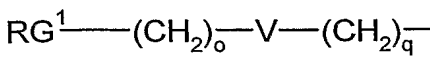
(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-but-3-inyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-but-3-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-but-3-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione.

In a compound of general formula (I) according to the invention that contains one of the above-mentioned elements, the hydrogen atoms in the above-mentioned elements are replaced in the positions indicated in formula (I) by radicals L^1-L^3, wherein radicals L^1-L^3 have the above-indicated meanings.

The invention also relates to linkers of general formula III^1

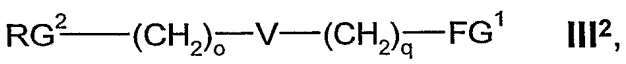


$$RG^1\text{——}(CH_2)_o\text{—}V\text{—}(CH_2)_q\text{—}FG^1 \qquad \mathbf{III^1},$$

in which

RG^1 can be an O=C=N group or an S=C=N group, and o, V, q and FG^1 have the meanings that are already mentioned above,

as well as linkers of general formula III^2

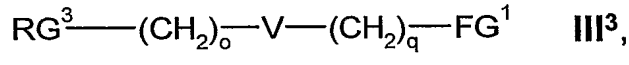


III^2,

in which

RG^2 can be a Hal-C(=T)-CHR^{22} group or a Hal-C(=T)-CHR^{22}-NR^{23}-C(=T) group or an R^{26}-C(=O)-O-C(=T)-CHR^{22} group or an R^{26}-C(=O)-O-C(=T)-CHR^{22}-NR^{23}-C(=T) group; R^{26} can be C_1-C_{10} alkyl, aryl, or aralkyl, and o, V, q, T and FG^1 have the meanings that are already mentioned above,

as well as linkers of general formula III^3



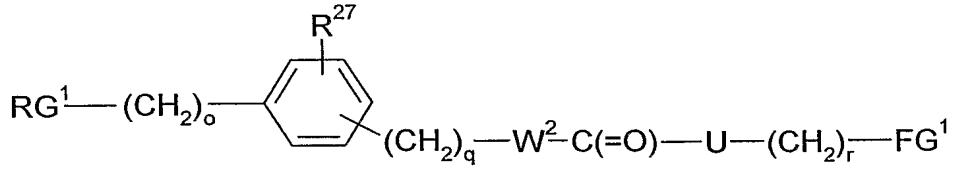
III^3,

in which

RG^3 can be an OH group or an NHR^{24a} group or a COOH group, and o, V, q and FG^1 have the meanings that are already mentioned above;

but with the proviso that the compound 1-(4-amino-phenyl)-pyrrole-2,5-dione is not included.

The invention also relates to linkers of general formula (IV^1):



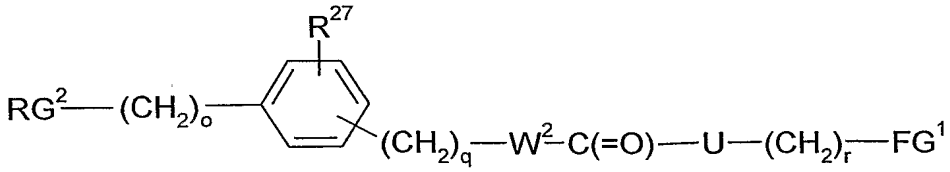
IV^1

,

in which

RG^1 is an O=C=N group or an S=C=N group, and o, q, r, W^2, R^{27}, U and FG^1 have the meanings that are mentioned in claim 1;

or linkers of general formula (IV^2):



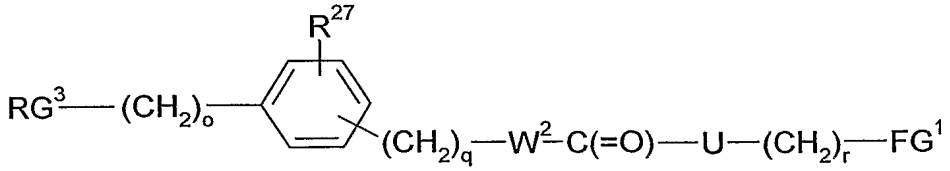
IV^2

,

in which

RG^2 is a Hal-C(=T)-CHR^{22} group or a Hal-C(=T)-CHR^{22}-NR^{23}-C(=T) group or an R^{26}-C(=O)-O-C(=T)-CHR^{22} group or an R^{26}-C(=O)-O-C(=T)-CHR^{22}-NR^{23}-C(=T) group, wherein R^{26} is C_1-C_{10} alkyl, aryl, or aralkyl, and R^{22}, R^{23}, T, o, q, r, W^2, R^{27}, U and FG^1 have the meanings that are mentioned in claim 1;

or linkers of general formula (IV^3):



IV^3

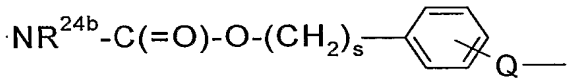
,

in which

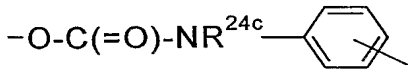
RG^3 is an OH group or an NHR^{24a} group or a COOH group, and R^{24a}, o, q, r, W^2, R^{27}, U and FG^1 have the meanings that are mentioned in claim 1.

According to the invention, linkers of general formulas III^1, III^2 or III^3 are preferred, wherein V represents a bond or an aryl radical, o is equal to zero, and T is an oxygen atom.

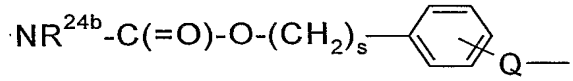
In addition, linkers of general formulas III^1, III^2 or III^3 according to the invention are preferred, in which V represents a bond or an aryl radical or a group



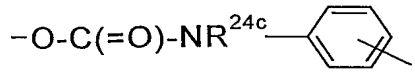
; Q represents a bond or a group



; and o is 0 to 4. Especially preferred from the above are those linkers in which V represents a bond or a group



; Q represents a bond or a group



; o is equal to 0, 2 or 3; s is equal to 1; and T is an oxygen atom.

In addition, preferred according to the invention are linkers of general formulas IV^1, IV^2 or IV^3, in which o is zero to four and q is zero to three. Especially preferred from the above are those linkers in which o is 0, 2 or 3; W^1 is an oxygen atom; q is equal to 0; R^{22} is hydrogen, C_1-C_3 alkyl or aralkyl; R^{23} is hydrogen or C_1-C_3 alkyl; R^{24a}

is hydrogen or C_1-C_3 alkyl; R^{27} is fluorine, chlorine, CN, NO_2, CO_2R^{28} or OR^{28}; R^{28} is hydrogen or C_1-C_5 alkyl; and U is oxygen, CHR^{22} or CHR^{22}-NR^{23}-C(=O).

Additionally, the invention relates to methods

to react a linker of general formula III^1 or IV^1 with a compound of general formula I, in which the condition that at least one group L^1, L^2 or L^4 represent a linker need not be met, and in which L^1 and/or L^2 and/or L^4 have the meaning of a hydrogen atom, and free hydroxyl groups and/or amino groups that are not required for the reaction optionally are protected,

to react a linker of general formula III^2 or IV^2 with a compound of general formula I, in which the condition that at least one group L^1, L^2 or L^4 represent a linker need not be met, and L^1 and/or L^2 and/or L^4 have the meaning of a hydrogen atom, and free hydroxyl groups and/or amino groups that are not required for the reaction are optionally protected, or

to react a linker of general formula III^3 or IV^3 with a compound of general formula I, in which the condition that at least one group L^1, L^2 or L^4 represent a linker need not be met, and L^1 and/or L^2 and/or L^4 have the meaning of a C(=O)Hal group or a C(=S)Hal group, and free hydroxyl groups and/or amino groups that are not required for the reaction are optionally protected.

The invention also relates to the use of a compound of general formula I, wherein the substituents have the above-mentioned meanings, but the condition that at least one substituent L^1, L^2 or L^4 represents a linker of general formula III or IV need not be met, and at least one substituent L^1, L^2 or L^4 represents hydrogen, a group C(=O)Cl, or a group C(S)Cl , in a method as described above.

The invention also relates to the use of a compound of general formula I, wherein the substituents have the above-mentioned meanings, but the condition that at least one substituent L^1, L^2 or L^4 represent a linker of general formula III or IV need not be met, and at least one substituent L^1, L^2 or L^4 represents hydrogen, a group C(=O)Cl, or a group C(S)Cl, for the production of an effector recognition unit conjugate as described above.

The invention also relates to the use of a linker of general formula III^1, III^2, III^3, IV^1, IV^2 or IV^3 for the production of an effector conjugate, as described above.

The invention also relates to the use of a linker of general formula III^1, III^2, III^3, IV^1, IV^2 or IV^3 for the production of an effector recognition unit conjugate as described above.

The invention also relates to the use of a recognition unit, as described above, in a process according to the invention for the production of an effector recognition unit conjugate, as described above.

The invention also relates to the effector recognition unit conjugates according to the invention for use as a medicament or for the production of a medicament or a pharmaceutical composition.

The invention relates finally to the use of the effector recognition unit conjugates according to the invention for the production of medicaments for the treatment of diseases that are associated with proliferative processes, such as tumors, inflammatory and/or neurodegenerative diseases, multiple sclerosis, Alzheimer's disease, or for the treatment of angiogenesis-associated diseases, such as tumor growth, rheumatoid arthritis or diseases of the ocular fundus.

Examples of the Synthesis of Linkers (L)

Example L1

(S) 2-[(3-Methyltrisulfanyl-propionyl)-methyl-amino]-propanoic acid

Example L1a

(S) 2-[(3-Acetylsulfanyl-propionyl)-methyl-amino]-propanoic acid ethyl ester

The solution of 15 g (89.5 mmol) of N-methylalanine ethyl ester-hydrochloride in 850 ml of anhydrous tetrahydrofuran is mixed at 23°C with 4.1 g of an approximately 60% sodium hydride dispersion and, after 3 hours, with 23.5 g of 3-acetylsulfanyl-propanoic acid chloride. It is allowed to react for two days, mixed with saturated sodium bicarbonate solution, and extracted several times with ethyl acetate. The combined organic extracts are washed with saturated sodium chloride solution, dried over sodium sulfate, and the residue that is obtained after filtration and removal of the solvent is purified by chromatography on fine silica gel. 17.6 g (67.3 mmol, 75%) of the title compound is isolated as a colorless oil.

Example L1b

(S) 2-[(3-Mercapto-propionyl)-methyl-amino]-propanoic acid

The solution of 17.6 g (67.3 mmol) of the compound prepared according to Example L1a in 150 ml of methanol is mixed at 23°C with 44 ml of a 5M sodium hydroxide solution, and it is stirred for 5 hours. By adding 4N hydrochloric acid, a pH of 2 is set, and it is extracted with dichloromethane. The combined organic extracts are washed with saturated sodium chloride solution and dried over sodium sulfate. The residue that is obtained after filtration and removal of the solvent (13.0 g, maximum 67.3 mmol) is further reacted without purification.

Example L1c

(S) 2-[(3-Mercapto-propionyl)-methyl-amino]-propanoic acid methyl ester

The solution of 4.53 g (maximum 23.7 mol) of the crude product, prepared according to Example L1b, in 135 ml of diethyl ether is esterified at 0°C with an ethereal solution of diazomethane. After removal of the solvent, 4.59 g (22.4 mmol,

94%) of the title compound is isolated as a pale yellow oil, which is further reacted without purification.

Example L1d

(S) 2-[(3-Methyltrisulfanyl-propionyl)-methyl-amino]-propanoic acid methyl ester

The solution of 14 g (68.2 mmol) of the compound, prepared according to Example L1c, in 180 ml of trichloromethane is added to the solution of 21 g of 2-methyldisulfanyl-isoindole-1,3-dione in 420 ml of trichloromethane, and it is stirred for 16 hours at 23°C. It is concentrated by evaporation, dissolved in dichloromethane, and stirred for 0.5 hour. Solid is filtered off, the filtrate is concentrated by evaporation, and the residue is purified by chromatography on fine silica gel. 16.2 g (57.2 mmol, 84%) of the title compound is isolated as a colorless oil.

Example L1

(S) 2-[(3-Methyltrisulfanyl-propionyl)-methyl-amino]-propanoic acid

The solution of 10 g (35.3 mmol) of the compound, prepared according to Example L1d, in 20 ml of ethanol is mixed with 1 l of phosphate puffer with a pH of 7, pig liver esterase, and it is incubated at 27°C for 46 hours. By adding a 4N hydrochloric acid, the pH is adjusted to 1, it is extracted with dichloromethane, dried over sodium sulfate, and after filtration and removal of the solvent, 8.3 g (30.8 mmol, 87%) of the title compound is isolated as a colorless oil, which is reacted without further purification.

^{1}H-NMR ($CDCl_3$): δ = 1.43+1.51 (3H), 2.55+2.63 (3H), 2.87 (2H), 2.88+3.00 (3H), 3.08-3.26 (2H), 4.63+5.19 (1H), 7.90 (1H) ppm.

Example L2

[(3-Methyltrisulfanyl-propionyl)-methyl-amino]-acetic acid

Example L2a

2-[(3-Acetylsulfanyl-propionyl)-methyl-amino]-acetic acid ethyl ester

7.13 g (46.4 mmol) of N-methylglycine ethyl ester-hydrochloride is reacted analogously to Example L1a, and 6.9 g (27.9 mmol, 60%) of the title compound is isolated as a colorless oil.

Example L2b

[(3-Mercapto-propionyl)-methyl-amino]-acetic acid

7.6 g (30.7 mmol) of the compound that is prepared according to Example L2a is reacted analogously to Example L1b, and 4.92 g (27.8 mmol, 90%) of the title compound is isolated as a colorless oil.

Example L2c

[(3-Mercapto-propionyl)-methyl-amino]-acetic acid methyl ester

4.92 g (27.8 mmol) of the compound that is prepared according to Example L2b is reacted analogously to Example L1c, and 5.01 g (26.2 mmol, 94%) of the title compound is isolated as a colorless oil.

Example L2d

[(3-Methyltrisulfanyl-propionyl)-methyl-amino]-acetic acid methyl ester

2.00 g (10.5 mmol) of the compound that is prepared according to Example L2c is reacted analogously to Example L1d, and 2.33 g (8.65 mmol, 82%) of the title compound is isolated as a colorless oil.

Example L2

[(3-Methyltrisulfanyl-propionyl)-methyl-amino]-acetic acid

2.00 g (7.83 mmol) of the compound that is prepared according to Example L2d is reacted analogously to Example L1, and 0.64 g (2.51 mmol, 32%) of the title compound is isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 2.41+2.56 (3H), 2.61-3.27 (7H), 3.98 (2H), 4.38 (1H) ppm.

Example L3

(S) 2-[(3-Methyltrisulfanyl-propionyl)-methyl-amino]-3-phenyl-propionic acid

Example L3a

(S) 2-[(3-Acetylsulfanyl-propionyl)-methyl-amino]-3-phenyl-propanoic acid ethyl ester

7.73 g (31.7 mmol) of N-methylphenylalanine ethyl ester-hydrochloride is reacted analogously to Example L1a, and 2.3 g (6.82 mmol, 22%) of the title compound is isolated as a colorless oil.

Example L3b

(S) 2-[(3-Mercapto-propionyl)-methyl-amino]-3-phenyl-propanoic acid

1.09 g (3.23 mmol) of the compound that is prepared according to Example L3a is reacted analogously to Example L1b, and 0.744 g (2.78 mmol, 86%) of the title compound is isolated as a colorless oil.

Example L3c

(S) 2-[(3-Mercapto-propionyl)-methyl-amino]-3-phenyl-propanoic acid methyl ester

0.74 g (2.77 mmol) of the compound that is prepared according to Example L3b is reacted analogously to Example L1c, and 0.77 g (2.74 mmol, 99%) of the title compound is isolated as a colorless oil.

Example L3d

(S) 2-[(3-Methyltrisulfanyl-propionyl)-methyl-amino]-3-phenyl-propanoic acid methyl ester

0.77 g (2.74 mmol) of the compound that is prepared according to Example L3c is reacted analogously to Example L1d, and 0.72 g (2.00 mmol, 73%) of the title compound is isolated as a colorless oil.

Example L3

(S) 2-[(3-Methyltrisulfanyl-propionyl)-methyl-amino]-3-phenyl-propanoic acid

0.72 g (2.00 mmol) of the compound that is prepared according to Example L3d is reacted analogously to Example L1, and 0.49 g (1.42 mmol, 71%) of the title compound is isolated as a colorless oil.

Example L4

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-butanoic acid

20.0 g (193.9 mmol) of 4-aminobutyric acid is mixed with 19 g of maleic acid anhydride, 290 ml of acetic acid, and it is heated for 4 hours in an oil bath at 130°C. It is azeotropically concentrated by evaporation with repeated addition of toluene, the residue is dissolved in dichloromethane and purified by chromatography on fine silica gel. 17.1 g (93.4 mmol, 48%) of the title compound is isolated as a crystalline solid.

^{1}H-NMR ($CDCl_3$): δ = 1.93 (2H), 2.38 (2H), 3.60 (2H), 6.71 (2H) ppm.

Example L4a

1-(3-Isocyanato-propyl)-pyrrole-2,5-dione

5.0 g (27.3 mmol) of the compound that is prepared according to Example L4 is dissolved in 90 ml of tetrahydrofuran, mixed with 8 ml of triethylamine and 6.17 ml of phosphoric acid diphenylester azide, and it is stirred for 1.5 hours at 23°C. Then, it is mixed with 110 ml of toluene, the tetrahydrofuran is distilled off, and it is heated for 2 hours to 70°C. The crude product is purified by chromatography on fine silica gel. 1.77 g (9.82 mmol, 36%) of the title compound is isolated.

Example L5

6-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-hexanoic acid

100 g (762 mmol) of 6-aminocaproic acid is reacted analogously to Example L5, and 93.8 g (444 mmol, 58%) of the title compound is isolated as a crystalline solid.

^{1}H-NMR ($CDCl_3$): δ = 1.34 (2H), 1.55-1.70 (4H), 2.34 (2H), 3.51 (2H), 6.69 (2H) ppm.

Example L5a

1-(5-Isocyanato-pentyl)-pyrrole-2,5-dione

10.0 g (47.3 mmol) of the compound that is prepared according to Example L5 is reacted analogously to Example L4a, and 3.19 g (15.3 mmol, 32%) of the title compound is isolated as a colorless oil.

Example L6

11-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-undecanoic acid

10 g (49.7 mmol) of 11-aminoundecanoic acid is reacted analogously to Example L5, and 6.29 g (22.4 mmol, 45%) of the title compound is isolated as a crystalline solid.

^{1}H-NMR ($CDCl_3$): δ = 1.19-1.36 (12H), 1.51-1.67 (4H), 2.34 (2H), 3.49 (2H), 6.68 (2H) ppm.

Example L6a

1-(10-Isocyanato-decyl)-pyrrole-2,5-dione

5.28 g (18.8 mmol) of the compound that is prepared according to Example L6 is reacted analogously to Example L4a, and 3.37 g (12.1 mmol, 64%) of the title compound is isolated as a colorless oil.

Example L7

1-(4-Amino-phenyl)-pyrrole-2,5-dione

The solution of 21.6 g (200 mmol) of 1,4-phenylenediamine in 200 ml of tetrahydrofuran is mixed over 1.5 hours with the solution of 19.6 g of maleic acid anhydride, and it is stirred for 22 hours at 23°C. It is filtered, rewashed with tetrahydrofuran, and the filtrate is dried. 37.1 g (197 mmol, 98%) of the title compound is isolated as a crystalline solid.

^{1}H-NMR (d6-DMSO): δ = 6.28 (1H), 6.48 (1H), 6.53 (2H), 7.30 (2H), 7.50-9.00 (2H) ppm.

Example L8

1-(4-Hydroxy-phenyl)-pyrrole-2,5-dione

The suspension that consists of 5.0 g (45.8 mmol) of 4-aminophenol, 4.49 g of maleic acid anhydride and 40 ml of acetic acid is refluxed for 3 hours. It is concentrated by evaporation, residual acetic acid is removed azeotropically by repeated distillation with acetic acid, and the residue is purified by chromatography on fine silica gel. 2.83 g (15.0 mmol, 33%) of the title compound is isolated.

^{1}H-NMR (d6-DMSO): δ = 6.83 (2H), 7.09 (2H), 7.13 (2H), 9.71 (1H) ppm.

Example L9

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-butanoic acid 4-hydroxymethyl-2-nitro-phenyl ester

The solution of 5.0 g (29.6 mmol) of 4-hydroxymethyl-2-nitro-phenol in 250 ml of dichloromethane is mixed with 6.1 g of N,N'-dicyclohexylcarbodiimide and 2.4 ml of pyridine, and the solution of 5.5 g of the compound, prepared according to Example L4, in 250 ml of dichloromethane, is added dropwise within 15 minutes. It is stirred for one more hour at 23°C, filtered, the filtrate is concentrated by evaporation and purified by chromatography on fine silica gel. 1.73 g (5.2 mmol, 18%) of the title compound is isolated.

^{1}H-NMR ($CDCl_3$): δ = 2.07 (3H), 2.67 (2H), 3.67 (2H), 4.79 (2H), 6.72 (2H), 7.28 (1H), 7.66 (1H), 8.10 (1H) ppm.

Example L10

6-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-hexanoic acid 4-hydroxymethyl-2-nitro-phenyl ester

Analogously to Example L9, 5.0 g (29.6 mmol) of 4-hydroxymethyl-2-nitro-phenol is reacted with 6.34 g of the compound that is prepared according to Example L5, and after working-up and purification, 3.78 g (10.4 mmol, 35%) of the title compound is isolated.

^{1}H-NMR ($CDCl_3$): δ = 1.42 (2H), 1.66 (2H), 1.88 (2H), 2.64 (2H), 3.55 (2H), 4.78 (2H), 6.69 (2H), 7.21 (1H), 7.64 (1H), 8.09 (1H) ppm.

Example L11

11-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-undecanoic acid 4-hydroxymethyl-2-nitro-phenyl ester

Analogously to Example L9, 5.0 g (29.6 mmol) of 4-hydroxymethyl-2-nitro-phenol is reacted with 8.44 g of the compound that is prepared according to Example L6, and after working-up and purification, 3.78 g (10.4 mmol, 35%) of the title compound is isolated.

^{1}H-NMR ($CDCl_3$): δ = 1.21-1.63 (14H), 1.76 (2H), 1.99 (1H), 2.63 (2H), 3.51 (2H), 4.78 (2H), 6.68 (2H), 7.21 (1H), 7.65 (1H), 8.10 (1H) ppm.

Example L12

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-butanoic acid 4-hydroxymethyl-phenyl ester

5.5 g (23,1 mmol) 4-tert-Butyldimethylsilanyloxymethyl-phenol, 20 mg N,N-Dimethyl-4-aminopyridine und 4.23 g (23,1 mmol) of the compound prepared according to Example L4 are dissolved in 92 ml of dichloromethane and cooled to 0°C. 4.77 g (23.1 mmol) N,N'-Dicyclohexylcarbodiimide in 24 ml dichloromethane are added dropwise to the cooled solution over a period of 15 min. The mixture is stirred for 16 hours at 23°C, filtered, the filtrate is concentrated and purified by chromatography on fine silica gel. 7.18 g (17.8 mmol, 77%) 4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-butanoic acid-4-tert-butyldimethylsilanyloxymethyl-phenyl ester are isolated. 1.42 g thereof are dissolved in 63 ml THF and 7 ml water, and 0.67g (3.52 mmol) p-toluenesulfonic acid are added at room temperature. After 16 hours, a saturated sodium bicarbonate solution is added and the mixture is extracted several times with ethyl acetate. The combined organic layers are washed with a saturated solution of sodium chloride, dried over sodium sulfate and purified by chromatography on fine silica gel. 0.43 g (1.5 mmol, 42%) of the title compound are isolated.

^{1}H-NMR ($CDCl_3$): δ = 1.71 (1H), 2.04 (2H), 2.58 (2H), 3.67 (2H), 4.68 (2H), 6.71 (2H), 7.09 (2H), 7.38 (2H) ppm.

Example L13

6-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-hexanoic acid 4-hydroxymethyl-phenyl ester

Analogously to Example L12, 4.02 g (13.8 mmol) 4-tert-butyldimethylsilanyloxymethyl- phenol are reacted with 3.56 g (13.8 mmol) of the compound prepared according to Example L5. After working-up, purification and analogous treatment with p-toluenesulfonic acid, 3,19 g (10.1 mmol, 60%) of the title compound are isolated.

^{1}H-NMR ($CDCl_3$): δ = 1.42 (2H), 1.59-1.83 (5H), 2.55 (2H), 3.55 (2H), 4.68 (2H), 6.69 (2H), 7.06 (2H), 7.38 (2H) ppm.

Example L14

11-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-undecanoic acid 4-hydroxymethyl-phenyl ester

Analogously to Example L12, 5.41 g (22.7 mmol) 4-tert-butyldimethylsilanyloxymethyl- phenol are reacted with 6.39 g (22.7 mmol) of the

compound prepared according to Example L6. After working-up, purification and analogous treatment with p-toluenesulfonic acid, 5.91 g (15.3 mmol, 67%) of the title compound are isolated.

^{1}H-NMR ($CDCl_3$): δ = 1.24-1.43 (12H), 1.57 (3H), 1.74 (2H), 2.55 (2H), 3.50 (2H), 4.69 (2H), 6.68 (2H), 7.06 (2H), 7.38 (2H) ppm.

Example L15

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-butanoic acid 4-hydroxymethyl-2-chloro-phenyl ester

Analogously to Example L9, 5.0 g (29.6 mmol) of 4-hydroxymethyl-2-chloro-phenol are reacted with 5.42 g of the compound prepared according to Example L4. After working-up and purification, 8.49 g (26.2 mmol, 89%) of the title compound are isolated.

^{1}H-NMR ($CDCl_3$): δ = 2.07 (3H), 2.64 (2H), 3.67 (2H), 4.67 (2H), 6.72 (2H), 7.14 (1H), 7.27 (1H), 7.46 (1H) ppm.

Example L16

6-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-hexanoic acid 4-hydroxymethyl-2-chloro-phenyl ester

Analogously to Example L9, 5.0 g (29.6 mmol) of 4-hydroxymethyl-2-chloro-phenol are reacted with 6.24 g of the compound prepared according to Example L5. After working-up and purification, 5.11 g (14.5 mmol, 49%) of the title compound are isolated.

^{1}H-NMR ($CDCl_3$): δ = 1.43 (2H), 1.66 (2H), 1.81 (3H), 2.61 (2H), 3.55 (2H), 4.67 (2H), 6.69 (2H), 7.10 (1H), 7.26 (1H), 7.46 (1H) ppm.

Example L17

11-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-undecanoic acid 4-hydroxymethyl-2-chloro-phenyl ester

Analogously to Example L9, 4.61 g (29 mmol) 4-hydroxymethyl-2-chloro-phenol are reacted with 8.17 g of the compound prepared according to Example L6. After working-up and purification, 4.61 g (10.9 mmol, 38%) of the title compound are isolated.

^{1}H-NMR ($CDCl_3$): δ= 1.18-1.84 (17H), 2.61 (2H), 3.51 (2H), 4.67 (2H), 6.68 (2H), 7.10 (1H), 7.27 (1H), 7.46 (1H) ppm.

Example L18

1-(6-Hydroxy-hexyl)-pyrrol-2,5-dione

26 ml of a 1,0M solution of borane-tetrahydrofurane-complex in tetrahydrofurane is added to a solution of 5.0 g (23.7 mmol) of the acid prepared according to Example L5 in 50 ml of anhydrous tetrahydrofurane and the mixture is stirred for 3 hours at 23°C. The mixture is poured into a saturated solution of sodium bicarbonate, extracted several times with ethyl acetate, and the combined organic extracts are dried over sodium sulfate. After filtration and removal of the solvent, the residue is purified by chromatography. 2.53 g (12.8 mmol, 54%) of the title compound are isolated.

^{1}H-NMR ($CDCl_3$): δ= 1.24-1.65 (9H), 3.52 (2H), 3.63 (2H), 6.68 (2H) ppm.

Examples of the Synthesis of Effector-Linker Conjugates (EL)

Example EL1

(4S,7R,8S,9S,13Z,16S)-[3-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-propyl]-carbamic acid-7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yl ester

Example EL1a

(4S,7R,8S,9S,13Z,16S)-7-Allyl-8-(*tert*-butyl-dimethyl-silanyloxy)-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione

The solution of 6.0 g (7.93 mmol) of (4S,7R,8S,9S,13Z,16S)-7-allyl-4,8-bis(*tert*-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione, which was produced analogously to the process that is described in WO 00/66589, in 186 ml of anhydrous dichloromethane is mixed at 0°C with 26.4 ml of a 20% solution of trifluoroacetic acid in dichloromethane, and it is stirred for 6 hours at 0°C. It is poured into saturated sodium bicarbonate solution, extracted with dichloromethane, the combined organic extracts are washed with water and dried over magnesium sulfate. The residue that is obtained after filtration and removal of the solvent is purified by chromatography on fine silica gel. 3.32 g (5.17 mmol, 65%) of the title compound is isolated as a colorless solid.

^{1}H-NMR ($CDCl_3$): δ = 0.09 (3H), 0.12 (3H), 0.93 (9H), 1.00 (3H), 1.06 (3H), 1.22 (3H), 1.70 (3H), 1.03-1.77 (5H), 1.95 (1H), 2.31-2.56 (6H), 2.83 (3H), 2.87 (1H), 3.00 (1H), 3.30 (1H), 3.90 (1H), 4.09 (1H), 4.94-5.03 (2H), 5.20 (1H), 5.77 (1H), 5.88 (1H), 7.34 (1H), 7.78 (1H), 7.95 (1H) ppm.

Example EL1b

(4S,7R,8S,9S,13Z,16S)-3-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-propyl]-carbamic acid-7-allyl-8-*tert*-butyl-dimethylsilyloxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yl ester

50 mg (78 µmol) of the compound that is prepared according to Example EL1a is dissolved in a mixture of 1.5 ml of trichloromethane and 1.5 ml of dimethylformamide, mixed with 144 mg of the linker that is prepared according to

Example L4a, 79 mg of copper(I) chloride, and it is heated for 18 hours to 70°C. The crude mixture is purified by chromatography on thin-layer plates, and 51 mg (62 µmol, 80%) of the title compound is isolated as a colorless oil.

Example EL1

(4S,7R,8S,9S,13Z,16S)-[3-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-propyl]-carbamic acid-7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yl ester

The solution of 41 mg (50 µmol) of the compound, prepared according to Example 1b, in a mixture of 0.8 ml of tetrahydrofuran and 0.8 ml of acetonitrile is mixed with 310 µl of hexafluorosilicic acid, 310 µl of hydrogen fluoride-pyridine complex, and it is stirred for 23 hours at 23°C. It is poured into a 5% sodium hydroxide solution, extracted with ethyl acetate, the combined organic extracts are washed with a saturated sodium chloride solution and dried over sodium sulfate. The residue that is obtained after filtration and removal of the solvent is purified by chromatography on thin-layer plates, and 26 mg (36.7 µmol, 73%) of the title compound is isolated as a colorless foam.

^{1}H-NMR ($CDCl_3$): δ = 0.99 (3H), 1.14 (3H), 1.17 (3H), 1.20-1.51 (3H), 1.54-1.87 (6H), 1.70 (3H), 2.22 (1H), 2.28-3.02 (9H), 2.83 (3H), 3.31 (1H), 3.45 (1H), 3.68 (1H), 4.44+4.83 (1H), 4.99 (1H), 5.03 (1H), 5.15 (1H), 5.61 (1H), 5.72 (1H), 5.91 (1H), 6.68 (2H), 7.36 (1H), 7.78 (1H), 7.90 (1H) ppm.

Example EL2

(1S,3S,7S,10R,11S,12S,16R)-[3-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-propyl]-carbamic acid-10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadec-7-yl ester (A) and

(1R,3S,7S,10R,11S,12S,16S)-[3-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-propyl]-carbamic acid-10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadec-7-yl ester (B)

The solution of 44 mg (62.2 µmol) of the compound, prepared according to Example 1, in 2.0 ml of dichloromethane is cooled to -50°C and mixed in portions over a period of 1.5 hours with a total of 1.7 ml of an approximately 0.1 M solution of dimethyl dioxiran in acetone. It is poured into a saturated sodium thiosulfate solution,

extracted with dichloromethane, and the combined organic extracts are dried over sodium sulfate. The residue that is obtained after filtration and removal of the solvent is purified by chromatography on thin-layer plates, and 22.7 mg (31.4 µmol, 50%) of title compound A as well as 7.6 mg (10.5 µmol, 17%) of title compound B are isolated in each case as a colorless foam.

^{1}H-NMR ($CDCl_3$) of A: δ = 1.01 (3H), 1.14 (3H), 1.16 (3H), 1.20-1.94 (8H), 1.32 (3H), 2.11-2.74 (9H), 2.82 (1H), 2.84 (3H), 3.30 (2H), 3.48 (2H), 3.68 (1H), 4.36+4.93 (1H), 4.99 (1H), 5.04 (1H), 5.54 (1H), 5.69 (1H), 6.05 (1H), 6.68 (2H), 7.32 (1H), 7.80 (1H), 7.88 (1H) ppm.

^{1}H-NMR ($CDCl_3$) of B: δ = 1.02 (6H), 1.26 (3H), 1.33 (1H), 1.23-2.27 (12H), 2.54-2.78 (4H), 2.82 (3H), 2.91 (1H), 3.13 (1H), 3.40 (2H), 3.66 (1H), 4.11 (1H), 4.84 (1H), 4.95 (1H), 5.01 (1H), 5.70 (1H), 5.81+5.93 (1H), 6.04+6.13 (1H), 6.69 (2H), 7.35 (1H), 7.75 (1H), 7.90+7.99 (1H) ppm.

Example EL3
(4S,7R,8S,9S,13Z,16S)-[5-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-pentyl]-carbamic acid-7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yl ester

Example EL3a
(4S,7R,8S,9S,13Z,16S)-[5-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-pentyl]-carbamic acid-7-allyl-8-*tert*-butyl-dimethylsilyloxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yl ester

50 mg (78 µmol) of the compound that is prepared according to Example EL1a is reacted analogously to Example EL1b with the linker that is produced according to Example L5a, and after purification, 39 mg (45.9 µmol, 59%) of the title compound is isolated as a colorless oil.

Example EL3
(4S,7R,8S,9S,13Z,16S)-[5-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-pentyl]-carbamic acid-7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yl ester

84 mg (98.8 µmol) of the compound that is prepared according to Example EL3a is reacted analogously to Example EL1, and after purification, 43 mg (58.4 µmol, 59%) of the title compound is isolated as a colorless foam.

^{1}H-NMR ($CDCl_3$): δ = 0.89 (3H), 0.96 (3H), 0.85-1.97 (17H), 1.12 (3H), 2.16-3.01 (10H), 2.82 (3H), 3.44 (1H), 3.65 (1H), 4.41+4.53 (1H), 4.98 (1H), 5.03 (1H), 5.15 (1H), 5.60 (1H), 5.71 (1H), 5.90 (1H), 6.68 (2H), 7.35 (1H), 7.77 (1H), 7.89+7.96 (1H) ppm.

Example EL4

(1S,3S,7S,10R,11S,12S,16R)-[5-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-pentyl]-carbamic acid-10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadec-7-yl ester (A) and (1R,3S,7S,10R,11S,12S,16S)-[5-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-pentyl]-carbamic acid-10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadec-7-yl ester (B)

26 mg (35.3 µmol) of the compound that is prepared according to Example EL3 is reacted analogously to Example EL2, and after purification, 9.1 mg (12.1 µmol, 34%) of title compound A as well as 3.0 mg (4.0 µmol, 11%) of title compound B are isolated in each case as a colorless foam.

^{1}H-NMR ($CDCl_3$) of A: δ = 0.83-1.94 (15H), 0.98 (3H), 1.14 (3H), 1.16 (3H), 1.32 (3H), 2.15-2.82 (8H), 2.84 (3H), 3.44 (2H), 3.51 (1H), 3.66 (1H), 4.46 (1H), 4.99 (1H), 5.04 (1H), 5.54 (1H), 5.69 (1H), 6.06 (1H), 6.68 (2H), 7.33 (1H), 7.80 (1H), 7.89 (1H) ppm.

^{1}H-NMR ($CDCl_3$) of B: δ = 0.78-2.74 (23H), 1.01 (3H), 1.03 (3H), 1.33 (3H), 2.82 (3H), 2.91 (1H), 3.14 (1H), 3.39 (1H), 3.47 (2H), 3.67 (1H), 4.12 (1H), 4.49 (1H), 4.92-5.06 (2H), 5.53+5.80 (1H), 5.69 (1H), 6.11 (1H), 6.68 (2H), 7.34 (1H), 7.74+7.79 (1H), 7.89+8.02 (1H) ppm.

Example EL5

(4S,7R,8S,9S,13Z,16S)-[10-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-decyl]-carbamic acid-7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yl ester

Example EL5a

(4S,7R,8S,9S,13Z,16S)-[10-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-decyl]-carbamic acid-7-allyl-8-*tert*-butyl-dimethylsilyloxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yl ester

50 mg (78 µmol) of the compound that is prepared according to Example EL1a is reacted analogously to Example EL1b with the linker that is produced according to Example L6a, and after purification, 56 mg (60.8 µmol, 78%) of the title compound is isolated as a colorless oil.

Example EL5

(4S,7R,8S,9S,13Z,16S)-[10-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-decyl]-carbamic acid-7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yl ester

20 mg (21.7 µmol) of the compound that is prepared according to Example EL5a is reacted analogously to Example EL1, and after purification, 10 mg (12.4 µmol, 57%) of the title compound is isolated as a colorless foam.

^{1}H-NMR ($CDCl_3$): δ = 0.91-1.87 (22H), 0.97 (3H), 1.13 (3H), 1.17 (3H), 1.70 (3H), 2.18-2.69 (8H), 2.80 (1H), 2.82 (3H), 2.96 (1H), 3.47 (1H), 3.50 (2H), 3.66 (1H), 3.97+4.36 (1H), 4.98 (1H), 5.04 (1H), 5.16 (1H), 5.61 (1H), 5.72 (1H), 5.91 (1H), 6.68 (2H), 7.37 (1H), 7.77 (1H), 7.90+7.97 (1H) ppm.

Example EL6

(1S,3S,7S,10R,11S,12S,16R)-[10-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-decyl]-carbamic acid-10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadec-7-yl ester (A) and

(1R,3S,7S,10R,11S,12S,16S)-[10-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-decyl]-carbamic acid-10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadec-7-yl ester (B)

18 mg (22 µmol) of the compound that is prepared according to Example EL5 is reacted analogously to Example EL2, and after purification, 9.2 mg (11.2 µmol, 51%) of title compound A as well as 3.2 mg (3.9 µmol, 18%) of title compound B are isolated in each case as a colorless foam.

^{1}H-NMR ($CDCl_3$) of A: δ = 0.98 (3H), 1.14 (3H), 1.16 (3H), 1.32 (3H), 1.03-1.67 (21H), 1.71-1.94 (3H), 2.18-2.78 (9H), 2.83 (3H), 3.50 (3H), 3.66 (1H), 3.87+4.43 (1H), 4.98 (1H), 5.04 (1H), 5.53 (1H), 5.69 (1H), 6.07 (1H), 6.68 (2H), 7.33 (1H), 7.80 (1H), 7.89+7.93 (1H) ppm.

^{1}H-NMR ($CDCl_3$) of B: δ = 0.80-1.64 (21H), 1.01 (3H), 1.03 (3H), 1.25 (3H), 1.33 (3H), 1.79-2.25 (5H), 2.34+3.14 (1H), 2.52-2.76 (4H), 2.81 (3H), 2.91 (1H), 3.40 (1H), 3.51 (2H), 3.67+3.82 (1H), 4.13+4.26 (1H), 4.46 (1H), 4.94 (1H), 5.01 (1H), 5.70 (1H), 5.81+5.94 (1H), 6.05+6.12 (1H), 6.68 (2H), 7.36 (1H), 7.74 (1H), 7.91+8.02 (1H) ppm.

Example EL7

(4S,7R,8S,9S,13Z,16S)-[3-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-propyl]-carbamic acid-7-allyl-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yl ester

Example EL7a

(4S,7R,8S,9S,13Z,16S)-7-Allyl-4-(*tert*-butyl-dimethyl-silanyloxy)-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione

The solution of 5.3 g (7.01 mmol) of (4S,7R,8S,9S,13Z,16S)-7-allyl-4,8-bis(*tert*-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione, which was produced analogously to the process described in WO 00/66589, in a mixture of 85 ml of tetrahydrofuran and 85 ml of acetonitrile, is mixed with 31.7 ml of hexafluorosilicic acid, cooled to 0°C, 8.1 ml of trifluoroacetic acid is added dropwise, and it is stirred for 20 hours at 0°C. It is poured into water, neutralized by adding a saturated sodium bicarbonate solution and extracted several times with ethyl acetate. The combined organic extracts are washed with saturated sodium chloride solution, dried over sodium sulfate, and the residue that is obtained after filtration and removal of the solvent is purified by chromatography on fine silica gel. 2.82 g (4.39 mmol, 63%) of the title compound is isolated as a colorless solid.

^{1}H-NMR ($CDCl_3$): δ = -0.09 (3H), 0.08 (3H), 0.84 (9H), 1.08 (3H), 1.10 (3H), 1.12 (3H), 1.21-1.86 (5H), 1.70 (3H), 2.15 (1H), 2.29-2.97 (8H), 2.84 (3H), 3.14 (1H),

3.96 (1H), 4.03 (1H), 4.97-5.06 (2H), 5.23 (1H), 5.61 (1H), 5.77 (1H), 7.35 (1H), 7.79 (1H), 7.93 (1H) ppm.

Example EL7b

(4S,7R,8S,9S,13Z,16S)-[3-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-propyl]-carbamic acid-7-allyl-4-*tert*-butyl-dimethylsilyloxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yl ester

100 mg (156 µmol) of the compound that is prepared according to Example EL7a is reacted analogously to Example EL1b with the linker that is produced according to Example L4a, and after purification, 121 mg (147 µmol, 94%) of the title compound is isolated as a colorless oil.

Example EL7

(4S,7R,8S,9S,13Z,16S)-[3-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-propyl]-carbamic acid-7-allyl-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yl ester

46 mg (56 µmol) of the compound that is prepared according to Example EL7b is reacted analogously to Example EL1, and after purification, 17 mg (24 µmol, 43%) of the title compound is isolated as a colorless foam.

^{1}H-NMR ($CDCl_3$): δ = 0.99-1.30 (2H), 1.03 (3H), 1.07 (3H), 1.21 (3H), 1.51-1.97 (6H), 1.72 (3H), 2.27-2.61 (6H), 2.83 (3H), 2.88 (1H), 3.09 (1H), 3.14 (2H), 3.51 (1H), 3.58 (2H), 4.04 (1H), 4.96-5.04 (2H), 5.12 (1H), 5.19 (1H), 5.28 (1H), 5.75 (1H), 5.86 (1H), 6.66 (2H), 7.35 (1H), 7.78 (1H), 7.96 (1H) ppm.

Example EL8

(1S,3S,7S,10R,11S,12S,16R)-[3-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-propyl]-carbamic acid-10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadec-11-yl ester (A) and

(1S,3S,7S,10R,11S,12S,16R)-[3-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-propyl]-carbamic acid-10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxabicyclo[14.1.0]-heptadec-11-yl ester (B)

29 mg (41 µmol) of the compound that is prepared according to Example EL7 is reacted analogously to Example EL2, and after purification, 18 mg (24.9 µmol, 61%) of title compound A as well as 3.0 mg (4.1 µmol, 10%) of title compound B are isolated in each case as a colorless foam.

^{1}H-NMR ($CDCl_3$) of A: δ = 0.98 (3H), 1.05 (3H), 1.24 (3H), 1.26 (3H), 1.12-1.83 (9H), 2.12-2.46 (4H), 2.59 (2H), 2.76 (1H), 2.84 (3H), 3.14 (2H), 3.59 (3H), 3.98 (1H), 4.10 (1H), 4.95-5.02 (2H), 5.17 (2H), 5.77 (1H), 6.19 (1H), 6.70 (2H), 7.38 (1H), 7.82 (1H), 7.97 (1H) ppm.

^{1}H-NMR ($CDCl_3$) of B: δ = 0.96 (3H), 1.01 (3H), 1.13-1.86 (11H), 1.28 (3H), 1.32 (1H), 2.16-2.50 (6H), 2.84 (3H), 3.02 (1H), 3.15 (2H), 3.50 (1H), 3.61 (2H), 3.88 (1H), 4.19 (1H), 4.96-5.04 (2H), 5.13 (1H), 5.28 (1H), 5.78 (1H), 6.33 (1H), 6.71 (2H), 7.36 (1H), 7.81 (1H), 7.96 (1H) ppm.

Example EL9

(4S,7R,8S,9S,13Z,16S)-[5-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-pentyl]-carbamic acid-7-allyl-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yl ester

Example EL9a

(4S,7R,8S,9S,13Z,16S)-[5-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-pentyl]-carbamic acid-7-allyl-4-*tert*-butyl-dimethylsilyloxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yl ester

100 mg (156 µmol) of the compound that is prepared according to Example EL7a is reacted analogously to Example EL1b with the linker that is produced according to Example L5a, and after purification, (65.9 µmol, 42%) of the title compound is isolated as a colorless oil.

Example EL9

(4S,7R,8S,9S,13Z,16S)-[5-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-pentyl]-carbamic acid-7-allyl-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yl ester

56 mg (65.9 µmol) of the compound that is prepared according to Example EL7b is reacted analogously to Example EL1, and after purification, 24.7 mg (33.6 µmol, 51%) of the title compound is isolated as a colorless foam.

^{1}H-NMR ($CDCl_3$): δ = 0.97-1.84 (11H), 1.02 (3H), 1.07 (3H), 1.20 (3H), 1.71 (3H), 1.91 (1H), 2.27-2.57 (6H), 2.84 (3H), 2.88 (1H), 2.95 (1H), 3.16 (2H), 3.51 (3H), 4.02 (1H), 4.46+4.83 (1H), 4.94-5.03 (2H), 5.15 (1H), 5.20 (1H), 5.74 (1H), 5.84 (1H), 6.68 (2H), 7.35 (1H), 7.80 (1H), 7.96 (1H) ppm.

Example EL10

(1S,3S,7S,10R,11S,12S,16R)-[5-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-pentyl]-carbamic acid-10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadec-11-yl ester (A) and (1S,3S,7S,10R,11S,12S,16R)-[5-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-pentyl]-carbamic acid-10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxabicyclo[14.1.0]hepta-dec-11-yl ester (B)

24.7 mg (33.6 µmol) of the compound that is prepared according to Example EL9 is reacted analogously to Example EL2, and after purification, 16.7 mg (22.2 µmol, 66%) of title compound A as well as 2.0 mg (2.7 µmol, 8%) of title compound B are isolated in each case as a colorless foam.

^{1}H-NMR ($CDCl_3$) of A: δ = 0.98 (3H), 1.04 (3H), 1.10-1.75 (13H), 1.23 (3H), 1.26 (3H), 2.09-2.62 (6H), 2.75 (1H), 2.84 (3H), 3.15 (2H), 3.51 (2H), 3.57 (1H), 3.99 (1H), 4.08 (1H), 4.46+4.74 (1H), 4.93-5.02 (2H), 5.18 (1H), 5.76 (1H), 6.18 (1H), 6.68 (2H), 7.38 (1H), 7.82 (1H), 7.97 (1H) ppm.

^{1}H-NMR ($CDCl_3$) of B: δ = 0.83-1.85 (13H), 0.95 (3H), 1.01 (3H), 1.27 (3H), 1.32 (3H), 2.17-2.49 (6H), 2.84 (3H), 3.03 (1H), 3.17 (2H), 3.48 (1H), 3.53 (2H), 3.86 (1H), 4.18 (1H), 4.66 (1H), 4.94-5.03 (2H), 5.27 (1H), 5.76 (1H), 6.33 (1H), 6.69 (2H), 7.35 (1H), 7.81 (1H), 7.96 (1H) ppm.

Example EL11

(1S,3S(E),7S,10R,11S,12S,16R)-[3-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-propyl]-carbamic acid 7-[3-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-propylcarbamoyloxy]-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-thiazol-4-yl)-vinyl]-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yl ester

10 mg (19.7 µmol) of (1S,3S(E),7S,10R,11S,12S,16R)-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-thiazol-4-yl)-vinyl]-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadecane is reacted analogously to Example EL1b with the linker that is produced according to Example L4a, and after purification, 7 mg (8.06 µmol, 41%) of the title compound is isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.88-2.20 (13H), 1.03 (3H), 1.05 (3H), 1.10 (3H), 1.24 (3H), 1.28 (3H), 2.08 (3H), 2.63-2.85 (4H), 2.71 (3H), 2.99-3.25 (3H), 3.41-3.50 (3H), 3.62 (2H), 4.88-5.70 (5H), 6.52 (1H), 6.69 (2H), 6.71 (2H), 7.02 (1H) ppm.

Example EL12

(4S,7R,8S,9S,13Z,16S)-Carbonic acid 7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yl ester 4-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-phenyl ester

Example EL12a

(4S,7R,8S,9S,13Z,16S)-Chloroformic acid-7-allyl-8-(*tert*-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yl ester

The solution of 1.0 g (1.56 mmol) of the compound, prepared according to Example EL1a, in 20 ml of dichloromethane is mixed at 0°C with the solution of 285 mg of triphosgene in 6 ml of dichloromethane, 160 µl of pyridine, and it is stirred for 2.5 hours at 23°C. It is concentrated by evaporation, the residue is dissolved in ethyl acetate, washed with water and saturated sodium chloride solution, and dried over magnesium sulfate. The residue that is obtained after filtration and removal of the solvent is purified by chromatography on fine silica gel. 1.08 g (1.53 mmol, 98%) of the title compound is isolated.

Example EL12b

(4S,7R,8S,9S,13Z,16S)-Carbonic acid 7-allyl-8-(*tert*-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yl ester 4-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-phenyl ester

The solution of 267 mg (370 µmol) of the compound, prepared according to Example EL12a, in 16 ml of ethyl acetate, is mixed with 51 µl of triethylamine, 700 mg of the compound that is prepared according to Example L8, and it is stirred for 16 hours at 23°C. It is poured into water, extracted several times with ethyl acetate, the combined organic extracts are washed with saturated sodium chloride solution and dried over magnesium sulfate. The residue that is obtained after filtration and removal

of the solvent is purified by chromatography on fine silica gel. 188 mg (219 µmol, 59%) of the title compound is isolated.

Example EL12

(4S,7R,8S,9S,13Z,16S)-Carbonic acid 7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yl ester 4-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-phenyl ester

Analogously to Example EL1, 248 mg (289 µmol) of the compound that is prepared according to Example EL12a is reacted, and after working-up and purification, 149 mg (201 µmol, 69%) of the title compound is isolated.

^{1}H-NMR ($CDCl_3$): δ = 1.08 (3H), 1.14 (3H), 1.26 (3H), 1.04-1.90 (8H), 2.24-2.57 (6H), 2.68-2.99 (3H), 2.81 (3H), 3.45 (1H), 3.72 (1H), 5.02 (1H), 5.06 (1H), 5.17 (1H), 5.65 (1H), 5.74 (1H), 5.98 (1H), 6.79 (2H), 6.88 (2H), 7.21 (2H), 7.33 (1H), 7.64 (1H), 7.97 (1H) ppm.

Example EL13

(1S,3S,7S,10R,11S,12S,16R)-Carbonic acid-10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yl ester 4-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-phenyl ester

Analogously to Example EL2, 144 mg (194 µmol) of the compound that is prepared according to Example EL12 is reacted, and after working-up and purification, 89 mg (117 µmol, 60%) of the title compound is isolated.

^{1}H-NMR ($CDCl_3$): δ = 1.10 (3H), 1.14 (3H), 1.27 (3H), 1.32 (3H), 1.19-1.85 (7H), 2.08-2.89 (8H), 2.81 (3H), 3.50 (1H), 3.70 (1H), 5.02 (1H), 5.07 (1H), 5.58 (1H), 5.72 (1H), 6.10 (1H), 6.81 (2H), 6.88 (2H), 7.21 (2H), 7.31 (1H), 7.68 (1H), 7.93 (1H) ppm.

Example EL14

(4S,7R,8S,9S,13Z,16S)-Carbonic acid 7-allyl-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yl ester 4-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-phenyl ester

Example EL14a

(4S,7R,8S,9S,13Z,16S)-Chloroformic acid-7-allyl-4-(*tert*-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yl ester

Analogously to Example EL12a, 1.0 g (1.56 mmol) of the compound that is prepared according to Example EL7a is reacted, and 1.05 g (1.49 mmol, 96%) of the title compound is isolated.

Example EL14b

(4S,7R,8S,9S,13Z,16S)-Carbonic acid 7-allyl-4-(*tert*-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yl ester 4-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-phenyl ester

The solution of 313 mg (0.44 mmol) of the compound, prepared according to Example EL14a, in 19 ml of ethyl acetate is mixed with 840 mg of the compound that is prepared according to Example L8, 61.5 µl of triethylamine, and it is stirred for 16 hours at 23°C. It is mixed with water, extracted several times with ethyl acetate, the combined organic extracts are washed with saturated sodium chloride solution and dried over sodium sulfate. The residue that is obtained after filtration and removal of the solvent is purified by chromatography on fine silica gel. 298 mg (348 µmol, 79%) of the title compound is isolated.

Example EL14

(4S,7R,8S,9S,13Z,16S)-Carbonic acid 7-allyl-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yl ester 4-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-phenyl ester

Analogously to Example EL1, 304 mg (355 µmol) of the compound that is prepared according to Example EL14a is reacted, and after working-up and purification, 67 mg (90 µmol, 25%) of the title compound is isolated.

^{1}H-NMR ($CDCl_3$): δ = 1.09 (3H), 1.11 (3H), 0.84-2.02 (7H), 1.27 (3H), 1.72 (3H), 2.29-2.58 (6H), 2.84 (3H), 2.89 (1H), 2.96 (1H), 3.63 (1H), 4.03 (1H), 5.06 (2H), 5.23 (2H), 5.80 (1H), 5.85 (1H), 6.86 (2H), 7.30 (2H), 7.35 (1H), 7.39 (1H), 7.80 (1H), 7.96 (1H) ppm.

Example EL15

(1S,3S,7S,10R,11S,12S,16R)-Carbonic acid-10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yl ester 4-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-phenyl ester

Analogously to Example EL2, 67 mg (90 µmol) of the compound that is prepared according to Example EL14 is reacted, and after working-up and purification, 32 mg (42 µmol, 47%) of the title compound is isolated.

^{1}H-NMR ($CDCl_3$): δ = 1.05 (3H), 1.06 (3H), 1.25 (3H), 1.35 (3H), 1.21-1.90 (7H), 2.18 (2H), 2.33-2.67 (4H), 2.73 (1H), 2.85 (3H), 3.79 (1H), 4.11 (1H), 4.33 (1H), 5.02 (1H), 5.07 (1H), 5.31 (1H), 5.81 (1H), 6.27 (1H), 6.86 (2H), 7.29 (2H), 7.35-7.41 (3H), 7.83 (1H), 7.99 (1H) ppm.

Example EL16

(1S,3S(E),7S,10R,11S,12S,16R)-*N*-[1-({4-[2-(7,11-Dihydroxy-8,8,10,12,16-pentamethyl-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-3-yl)-propenyl]-thiazol-2-ylmethyl}-carbamoyl)-ethyl]-3-methyltrisulfanyl-*N*-methyl-propionamide

The solution of 7 mg (13 µmol) of (1S,3S(E),7S,10R,11S,12S,16R)-3-[2-(2-aminomethyl-thiazol-4-yl)-1-methyl-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione, which was produced analogously to the process described in WO 99/01124, in 0.5 ml of dichloromethane is mixed with 7 mg of the compound that is prepared according to Example L1, 0.4 mg of 4-dimethylaminopyridine and 4 mg of N,N'-dicyclohexylcarbodiimide are added, and it is stirred for 20 minutes at 23°C. Precipitated urea is filtered out, and it is purified by chromatography on a preparative thin-layer plate. 5 mg (6.5 µmol, 50%) of the title compound is isolated.

^{1}H-NMR ($CDCl_3$): δ = 1.00 (3H), 1.08 (3H), 1.17 (3H), 1.23-1.77 (5H), 1.28 (3H), 1.36 (3H), 1.39 (3H), 1.88-2.13 (3H), 2.10 (3H), 2.37 (1H), 2.49-2.66 (2H), 2.55 (3H), 2.77-2.92 (4H), 2.97 (3H), 3.16 (2H), 3.31 (1H), 3.77 (1H), 4.08 (1H), 4.19 (1H), 4.62 (1H), 4.76 (1H), 5.25 (1H), 5.45 (1H), 6.57 (1H), 7.01 (1H), 7.06 (1H) ppm.

Example EL17

(1S,3S(E),7S,10R,11S,12S,16R)-2-[Methyl-(3-methyltrisulfanyl-propionyl)-amino]-propionic acid-4-[2-(7,11-dihydroxy-8,8,10,12,16-pentamethyl-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-3-yl)-propenyl]-thiazol-2-ylmethyl ester

Analogously to Example EL16, 10 mg (19 µmol) of (1S,3S(E),7S,10R,11S, 12S,16R)-7,11-dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-1-methyl-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0] heptadecane-5,9-dione, which was produced analogously to the process that is described in WO 99/01124, is reacted, and 2.2 mg (2.8 µmol, 15%) of the title compound is isolated.

^{1}H-NMR ($CDCl_3$): δ = 1.01 (3H), 1.09 (3H), 1.18 (3H), 1.27 (1H), 1.28 (3H), 1.32-1.76 (3H), 1.37 (3H), 1.47 (3H), 1.95 (1H), 2.06 (1H), 2.12 (3H), 2.38 (1H), 2.51-2.63 (2H), 2.56 (3H), 2.78-2.92 (5H), 2.97+3.01 (3H), 3.13-3.35 (3H), 3.71 (1H), 3.77 (1H), 4.00 (1H), 4.18 (1H), 5.25 (1H), 5.39 (2H), 5.45 (1H), 6.60 (1H), 7.17 (1H) ppm.

Example EL18

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-butanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

Example EL18a

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-butanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-8-(*tert*-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

Analogously to Example EL12b, 200 mg (284 µmol) of the compound that is prepared according to Example EL12a is reacted with 770 mg of the compound that is prepared according to Example L9, and after working-up and purification, 129 mg (129 µmol, 45%) of the title compound is isolated.

Example EL18

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-butanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

Analogously to Example EL1, 129 mg (129 µmol) of the compound that is prepared according to Example EL18a is reacted, and after working-up and purification, 71 mg (80 µmol, 62%) of the title compound is isolated.

^{1}H-NMR ($CDCl_3$): δ = 0.88-2.11 (11H), 1.02 (3H), 1.14 (3H), 1.71 (3H), 2.23-2.56 (6H), 2.63-2.71 (3H), 2.74 (3H), 2.97 (1H), 3.39 (1H), 3.68 (3H), 4.58 (1H), 4.78 (1H), 5.01 (1H), 5.05 (1H), 5.18 (1H), 5.56 (1H), 5.71 (1H), 5.97 (1H), 6.73 (2H), 7.19 (1H), 7.31 (1H), 7.36 (1H), 7.75 (1H), 7.77 (1H), 7.95 (1H) ppm.

Example EL19

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-butanoic acid 4-(1S,3S,7S,10R,11S,12S,16R)-[10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yloxycarbonyloxymethyl]-2-nitro-phenyl ester (A) and 4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-butanoic acid 4-(1R,3S,7S,10R,11S,12S,16S)-[10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yloxycarbonyloxymethyl]-2-nitro-phenyl ester (B)

Analogously to Example EL2, 71 mg (80 µmol) of the compound that is prepared according to Example EL18 is reacted, and after working-up and purification, 41 mg (45 µmol, 57%) of title compound A as well as 12 mg (13 µmol, 17%) of title compound B are isolated.

^{1}H-NMR ($CDCl_3$) of A: δ = 1.04 (3H), 1.14 (3H), 1.16 (3H), 1.32 (3H), 1.34-1.84 (6H), 2.01-2.74 (12H), 2.78 (3H), 2.86 (1H), 3.44 (1H), 3.68 (3H), 4.56 (1H), 4.74 (1H), 5.01 (1H), 5.06 (1H), 5.47 (1H), 5.70 (1H), 6.07 (1H), 6.73 (2H), 7.20 (1H), 7.32 (1H), 7.36 (1H), 7.77 (1H), 7.81 (1H), 7.90 (1H) ppm.

Example EL20

6-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-hexanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

Example EL20a

6-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-hexanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-8-(*tert*-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

Analogously to Example EL12b, 243 mg (345 µmol) of the compound that is prepared according to Example EL12a is reacted with 1 g of the compound that is prepared according to Example L10, and after working-up and purification, 25 mg (24 µmol, 7%) of the title compound is isolated.

Example EL20

6-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-hexanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

Analogously to Example EL1, 212 mg (206 µmol) of the compound that is prepared according to Example EL20a is reacted, and after working-up and purification, 117 mg (128 µmol, 62%) of the title compound is isolated.

^{1}H-NMR ($CDCl_3$): δ = 1.01 (3H), 1.14 (6H), 1.04-2.78 (20H), 1.70 (3H), 2.74 (3H), 2.97 (1H), 3.39 (1H), 3.56 (2H), 3.68 (1H), 4.11 (1H), 4.58 (1H), 4.77 (1H), 5.00 (1H), 5.05 (1H), 5.18 (1H), 5.56 (1H), 5.71 (1H), 5.97 (1H), 6.69 (2H), 7.12 (1H), 7.29 (1H), 7.36 (1H), 7.75 (2H), 7.94 (1H) ppm.

Example EL21

6-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-hexanoic acid 4-(1S,3S,7S,10R,11S,12S,16R)-[10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yloxycarbonyloxymethyl]-2-nitro-phenyl ester (A) and 6-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-hexanoic acid 4-(1R,3S,7S,10R,11S,12S,16S)-[10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yloxycarbonyloxymethyl]-2-nitro-phenyl ester (B)

Analogously to Example EL2, 117 mg (128 µmol) of the compound that is prepared according to Example EL20 is reacted, and after working-up and purification, 63 mg (68 µmol, 53%) of title compound A as well as 19 mg (20 µmol, 16%) of title compound B are isolated.

^{1}H-NMR ($CDCl_3$) of A: δ = 1.03 (3H), 1.14 (3H), 1.15 (3H), 1.32 (3H), 1.07-2.75 (22H), 2.77 (3H), 2.86 (1H), 3.44 (1H), 3.55 (2H), 3.69 (1H), 4.55 (1H), 4.77 (1H), 5.01 (1H), 5.06 (1H), 5.47 (1H), 5.70 (1H), 6.08 (1H), 6.70 (2H), 7.14 (1H), 7.31 (1H), 7.35 (1H), 7.76 (1H), 7.80 (1H), 7.90 (1H) ppm.

Example EL22

11-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-undecanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

Example EL22a

11-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-undecanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-8-(*tert*-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

Analogously to Example EL12b, 243 mg (345 µmol) of the compound that is prepared according to Example EL12a is reacted with 1.19 g of the compound that is prepared according to Example L11, and after working-up and purification, 171 mg (155 µmol, 45%) of the title compound is isolated.

Example EL22

11-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-undecanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

Analogously to Example EL1, 171 mg (155 µmol) of the compound that is prepared according to Example EL22a is reacted, and after working-up and purification, 108 mg (110 µmol, 71%) of the title compound is isolated.

^{1}H-NMR ($CDCl_3$): δ = 1.02 (3H), 1.14 (6H), 0.88-2.56 (28H), 1.70 (3H), 2.63 (2H), 2.71 (1H), 2.74 (3H), 2.98 (1H), 3.39 (1H), 3.50 (2H), 3.69 (1H), 4.58 (1H), 4.77 (1H), 5.00 (1H), 5.05 (1H), 5.17 (1H), 5.56 (1H), 5.71 (1H), 5.97 (1H), 6.68 (2H), 7.11 (1H), 7.29 (1H), 7.36 (1H), 7.75 (1H), 7.76 (1H), 7.94 (1H) ppm.

Example EL23

11-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-undecanoic acid 4-(1S,3S,7S,10R,11S,12S,16R)-[10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yloxycarbonyloxymethyl]-2-nitro-phenyl ester (A) and 11-(2,5-Dioxo-2,5-dihydro-

pyrrol-1-yl)-undecanoic acid 4-(1R,3S,7S,10R,11S,12S, 16S)-[10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yloxycarbonyloxymethyl]-2-nitro-phenyl ester (B)

Analogously to Example EL2, 108 mg (110 µmol) of the compound that is prepared according to Example EL22 is reacted, and after working-up and purification, 65.9 mg (65.8 µmol, 60%) of title compound A as well as 19.8 mg (20 µmol, 18%) of title compound B are isolated.

^{1}H-NMR ($CDCl_3$) of A: δ = 1.04 (3H), 1.14 (3H), 1.15 (3H), 1.63 (3H), 0.92-1.85 (23H), 2.10-2.81 (9H), 2.77 (3H), 2.86 (1H), 3.45 (1H), 3.51 (2H), 3.69 (1H), 4.55 (1H), 4.74 (1H), 5.01 (1H), 5.06 (1H), 5.47 (1H), 5.70 (1H), 6.08 (1H), 6.68 (2H), 7.13 (1H), 7.31 (1H), 7.35 (1H), 7.77 (1H), 7.80 (1H), 7.90 (1H) ppm.

Example EL24

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-butanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

Example EL24a

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-butanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-4-(*tert*-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

Analogously to Example EL12b, 271 mg (385 µmol) of the compound that is prepared according to Example EL14a is reacted with 1.04 g of the compound that is prepared according to Example L9, and after working-up and purification, 193 mg (193 µmol, 50%) of the title compound is isolated.

Example EL24

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-butanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

Analogously to Example EL1, 193 mg (193 μmol) of the compound that is prepared according to Example EL24a is reacted, and after working-up and purification, 107 mg (120 μmol, 62%) of the title compound is isolated.

^{1}H-NMR ($CDCl_3$): δ = 1.02 (3H), 1.07 (3H), 1.23 (3H), 0.97-2.13 (8H), 1.71 (3H), 2.28-2.54 (6H), 2.67 (2H), 2.84 (3H), 2.88 (1H), 2.95 (1H), 3.56 (1H), 3.67 (2H), 4.01 (1H), 4.93 (1H), 4.98 (1H), 5.17 (1H), 5.22 (3H), 5.70 (1H), 5.84 (1H), 6.72 (2H), 7.30 (1H), 7.34 (1H), 7.69 (1H), 7.80 (1H), 7.95 (1H), 8.13 (1H) ppm.

Example EL25

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-butanoic acid 4-(1S,3S,7S,10R,11S,12S,16R)-[10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yloxycarbonyloxymethyl]-2-nitro-phenyl ester (A) and 4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-butanoic acid 4-(1R,3S,7S,10R,11S,12S,16S)-[10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yloxycarbonyloxymethyl]-2-nitro-phenyl ester (B)

Analogously to Example EL2, 102 mg (115 μmol) of the compound that is prepared according to Example EL19 is reacted, and after working-up and purification, 65 mg (72 μmol, 63%) of title compound A as well as 3 mg (3.3 μmol, 3%) of title compound B are isolated.

^{1}H-NMR ($CDCl_3$) of A: δ = 0.97 (3H), 1.04 (3H), 1.23 (3H), 1.31 (3H), 1.10-2.75 (18H), 2.85 (3H), 3.68 (2H), 3.71 (1H), 4.09 (1H), 4.28 (1H), 4.92 (1H), 4.97 (1H), 5.20 (2H), 5.23 (1H), 5.72 (1H), 6.26 (1H), 6.72 (2H), 7.30 (1H), 7.37 (1H), 7.68 (1H), 7.83 (1H), 7.98 (1H), 8.13 (1H) ppm.

Example EL26

6-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-hexanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

Example EL26a

6-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-hexanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-4-(*tert*-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-

benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

Analogously to Example EL12b, 273 mg (387 µmol) of the compound that is prepared according to Example EL14a is reacted with 1.12 g of the compound that is prepared according to Example L10, and after working-up and purification, 69 mg (67 µmol, 17%) of the title compound is isolated.

Example EL26

6-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-hexanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

Analogously to Example EL1, 69 mg (67 µmol) of the compound that is prepared according to Example EL26a is reacted, and after working-up and purification, 26 mg (28 µmol, 42%) of the title compound is isolated.

^{1}H-NMR ($CDCl_3$): δ = 0.93 (3H), 0.95 (3H), 1.16 (3H), 1.60 (3H), 0.98-2.61 (20H), 2.73 (3H), 2.77 (1H), 3.45 (3H), 3.83 (1H), 4.05 (1H), 4.83 (1H), 4.88 (1H), 5.05 (1H), 5.13 (3H), 5.62 (1H), 5.74 (1H), 6.61 (2H), 7.16 (1H), 7.26 (1H), 7.60 (1H), 7.70 (1H), 7.88 (1H), 8.03 (1H) ppm.

Example EL27

6-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-hexanoic acid 4-(1S,3S,7S,10R,11S,12S,16R)-[10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yloxycarbonyloxymethyl]-2-nitro-phenyl ester (A) and 6-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-hexanoic acid 4-(1R,3S,7S,10R,11S,12S,16S)-[10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yloxycarbonyloxymethyl]-2-nitro-phenyl ester (B)

Analogously to Example EL2, 38 mg (41 µmol) of the compound that is prepared according to Example EL19 is reacted, and after working-up and purification, 14 mg (15 µmol, 37%) of title compound A as well as 2 mg (2 µmol, 5%) of title compound B are isolated.

^{1}H-NMR ($CDCl_3$) of A: δ = 0.96 (3H), 1.03 (3H), 1.08-1.86 (13H), 1.23 (3H), 1.30 (3H), 2.16 (2H), 2.23-2.78 (7H), 2.83 (3H), 3.54 (2H), 3.71 (1H), 4.09 (1H), 4.27

(1H), 4.91 (1H), 4.96 (1H), 5.21 (3H), 5.72 (1H), 6.25 (1H), 6.69 (2H), 7.23 (1H), 7.36 (1H), 7.67 (1H), 7.82 (1H), 7.96 (1H), 8.11 (1H) ppm.

Example EL28

11-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-undecanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

Example EL28a

11-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-undecanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-4-(*tert*-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

Analogously to Example EL12b, 273 mg (387 µmol) of the compound that is prepared according to Example EL14a is reacted with 1.34 g of the compound that is prepared according to Example L11, and after working-up and purification, 196 mg (178 µmol, 46%) of the title compound is isolated.

Example EL28

11-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-undecanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

Analogously to Example EL1, 196 mg (178 µmol) of the compound that is prepared according to Example EL28a is reacted, and after working-up and purification, 100 mg (101 µmol, 57%) of the title compound is isolated.

^{1}H-NMR ($CDCl_3$): δ = 1.03 (3H), 1.06 (3H), 1.23 (3H), 1.70 (3H), 0.99-1.81 (21H), 1.91 (1H), 2.27-2.53 (6H), 2.63 (2H), 2.83 (3H), 2.88 (1H), 2.95 (1H), 3.51 (2H), 3.56 (1H), 4.00 (1H), 4.92 (1H), 4.98 (1H), 5.13-5.26 (4H), 5.71 (1H), 5.83 (1H), 6.68 (2H), 7.23 (1H), 7.34 (1H), 7.67 (1H), 7.79 (1H), 7.95 (1H), 8.13 (1H) ppm.

Example EL29

11-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-undecanoic acid 4-(1S,3S,7S,10R,11S,12S,16R)-[10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-

benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yloxycarbonyloxymethyl]-2-nitro-phenyl ester (A) and 11-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-undecanoic acid 4-(1R,3S,7S,10R,11S, 12S,16S)-[10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yloxycarbonyloxymethyl]-2-nitro-phenyl ester (B)

Analogously to Example EL2, 100 mg (101 µmol) of the compound that is prepared according to Example EL19 is reacted, and after working-up and purification, 21 mg (21 µmol, 21%) of title compound A as well as 2 mg (2 µmol, 2%) of title compound B are isolated.

^{1}H-NMR ($CDCl_3$) of A: δ = 0.97 (3H), 1.04 (3H), 1.23 (3H), 0.84-1.84 (24H), 1.71 (3H), 2.15 (2H), 2.23-2.68 (5H), 2.71 (1H), 2.83 (3H), 3.50 (2H), 3.71 (1H), 4.09 (1H), 4.27 (1H), 4.91 (1H), 4.96 (1H), 5.19 (2H), 5.23 (1H), 5.72 (1H), 6.26 (1H), 6.68 (2H), 7.23 (1H), 7.36 (1H), 7.66 (1H), 7.83 (1H), 7.97 (1H), 8.12 (1H) ppm.

Example EL30

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-butanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-phenyl ester

Example EL30a

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-butanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-8-(tert-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-phenyl ester

Analogously to Example EL12b, 218 mg (309 µmol) of the compound prepared according to Example EL12a are reacted with 314 mg of the compound prepared according to Example L12. After working-up and purification, 103 mg (118 µmol, 35%) of the title compound are isolated.

Example EL30

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-butanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-phenyl ester

Analogously to Example EL1, 103 mg (118 µmol) of the compound prepared according to Example EL30a are reacted. After working-up and purification, 13 mg (15 µmol, 13%) of the title compound are isolated.

^{1}H-NMR ($CDCl_3$): δ= 0.88-1.84 (7H), 1.00 (3H), 1.12 (3H), 1.14 (3H), 1.71 (3H), 2.04 (2H), 2.23-2.71 (8H), 2.74 (3H), 2.99 (1H), 3.40 (1H), 3.67 (3H), 4.48 (1H), 4.76 (1H), 5.00 (1H), 5.04 (1H), 5.18 (1H), 5.55 (1H), 5.71 (1H), 5.98 (1H), 6.72 (2H), 7.01 (2H), 7.08 (2H), 7.37 (1H), 7.76 (1H), 7.96 (1H) ppm.

Example EL31

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-butanoic acid 4-(1S,3S,7S,10R,11S,12S, 16R)-[10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yloxycarbonyloxymethyl]-phenyl ester

Analogously to Example EL2, 13 mg (15 µmol) of the compound prepared according to Example EL30 are reacted. After working-up and purification, 5.7 mg (6.6 µmol, 44%) of the title compound are isolated.

^{1}H-NMR ($CDCl_3$) of A: δ = 1.04 (3H), 1.14 (3H), 1.16 (3H), 1.32 (3H), 1.34-1.84 (6H), 2.04 (2H), 2.15-2.75 (10H), 2.78 (3H), 2.85 (1H), 3.44 (1H), 3.67 (3H), 4.48 (1H), 4.73 (1H), 5.01 (1H), 5.05 (1H), 5.47 (1H), 5.70 (1H), 6.07 (1H), 6.72 (2H), 7.02 (2H), 7.13 (2H), 7.31 (1H), 7.77 (1H), 7.93 (1H) ppm.

Example EL32

6-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-hexanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-phenyl ester

Example EL32a

6-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-hexanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-8-(tert-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-phenyl ester

Analogously to Example EL12b, 218 mg (309 µmol) of the compound prepared according to Example EL12a are reacted with 396 mg of the compound prepared according to Example L13. After working-up and purification, 157 mg (159 µmol, 51%) of the title compound are isolated.

Example EL32

6-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-hexanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-phenyl ester

Analogously to Example EL1, 157 mg (159 µmol) of the compound prepared according to Example EL32a are reacted. After working-up and purification, 32 mg (37 µmol, 23%) of the title compound are isolated.

^{1}H-NMR ($CDCl_3$): δ = 0.99 (3H), 1.12 (3H), 1.14 (3H), 1.04-2.84 (20H), 1.70 (3H), 2.75 (3H), 3.00 (1H), 3.40 (1H), 3.55 (2H), 3.68 (1H), 4.48 (1H), 4.76 (1H), 5.00 (1H), 5.04 (1H), 5.18 (1H), 5.55 (1H), 5.71 (1H), 5.98 (1H), 6.69 (2H), 6.98 (2H), 7.07 (2H), 7.37 (1H), 7.76 (2H), 7.96 (1H) ppm.

Example EL33

6-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-hexanoic acid 4-(1S,3S,7S,10R,11S,12S, 16R)-[10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yloxycarbonyloxymethyl]-phenyl ester

Analogously to Example EL2, 30 mg (34 µmol) of the compound prepared according to Example EL32 are reacted. After working-up and purification, 13 mg (15 µmol, 44%) of the title compound are isolated.

^{1}H-NMR ($CDCl_3$) of A: δ = 1.01 (3H), 1.13 (3H), 1.14 (3H), 1.32 (3H), 1.07-2.75 (22H), 2.78 (3H), 2.85 (1H), 3.44 (1H), 3.55 (2H), 3.69 (1H), 4.48 (1H), 4.73 (1H), 5.01 (1H), 5.05 (1H), 5.45 (1H), 5.70 (1H), 6.08 (1H), 6.69 (2H), 6.99 (2H), 7.12 (2H), 7.32 (1H), 7.77 (1H), 7.92 (1H) ppm.

Example EL34

11-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-undecanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-phenyl ester

Example EL34a

11-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-undecanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-8-(tert-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-phenyl ester

Analogously to Example EL12b, 218 mg (309 µmol) of the compound prepared according to Example EL12a are reacted with 422 mg of the compound prepared according to Example L14. After working-up and purification, 77 mg (73 µmol, 24%) of the title compound are isolated.

Example EL34

11-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-undecanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-phenyl ester

Analogously to Example EL1, 77 mg (73 µmol) of the compound prepared according to Example EL34a are reacted. After working-up and purification, 14 mg (15 µmol, 20%) of the title compound are isolated.

^{1}H-NMR ($CDCl_3$): δ = 0.99 (3H), 1.11 (3H), 1.14 (3H), 0.88-1.88 (22H), 1.70 (3H), 2.24-2.58 (8H), 2.67 (1H), 2.75 (3H), 3.00 (1H), 3.40 (1H), 3.51 (2H), 3.68 (1H), 4.48 (1H), 4.76 (1H), 5.00 (1H), 5.04 (1H), 5.18 (1H), 5.55 (1H), 5.71 (1H), 5.98 (1H), 6.68 (2H), 6.98 (2H), 7.07 (2H), 7.37 (1H), 7.76 (1H), 7.96 (1H) ppm.

Example EL35

11-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-undecanoic acid 4-(1S,3S,7S,10R,11S,12S,16R)-[10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yloxycarbonyloxymethyl]-phenyl ester

Analogously to Example EL2, 14 mg (15 µmol) of the compound prepared according to Example EL34 are reacted. After working-up and purification, 6 mg (6 µmol, 42%) of the title compound are isolated.

^{1}H-NMR ($CDCl_3$) von A: δ = 1.01 (3H), 1.14 (6H), 1.20-1.90 (26H), 2.12-2.58 (8H), 2.71 (1H), 2.77 (3H), 2.85 (1H), 3.44 (1H), 3.51 (2H), 3.69 (1H), 4.48 (1H), 4.73 (1H),

5.01 (1H), 5.05 (1H), 5.45 (1H), 5.70 (1H), 6.08 (1H), 6.68 (2H), 6.99 (2H), 7.12 (2H), 7.31 (1H), 7.77 (1H), 7.92 (1H) ppm.

Example EL36

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-butanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yloxycarbonyloxymethyl]-phenyl ester

Example EL36a

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-butanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-4-(tert-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yloxycarbonyloxymethyl]-phenyl ester

Analogously to Example EL12b, 330 mg (470 µmol) of the compound prepared according to Example EL14a are reacted with 544 mg of the compound prepared according to Example L12. After working-up and purification, 170 mg (178 µmol, 38%) of the title compound are isolated.

Example EL36

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-butanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yloxycarbonyloxymethyl]-phenyl ester

Analogously to Example EL1, 170 mg (178 µmol) of the compound prepared according to Example EL36a are reacted. After working-up and purification, 21 mg (24 µmol, 14%) of the title compound are isolated.

^{1}H-NMR ($CDCl_3$): δ = 1.02 (3H), 1.07 (3H), 1.22 (3H), 0.97-2.13 (8H), 1.70 (3H), 2.28-2.63 (8H), 2.84 (3H), 2.82-2.95 (2H), 3.55 (1H), 3.67 (2H), 3.97 (1H), 4.92 (1H), 4.96 (1H), 5.15 (1H), 5.16 (2H), 5.22 (1H), 5.70 (1H), 5.82 (1H), 6.68 (2H), 7.08 (2H), 7.34 (1H), 7.41 (2H), 7.79 (1H), 7.94 (1H) ppm.

Example EL37

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-butanoic acid 4-(1S,3S,7S,10R,11S,12S, 16R)-[10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-

4,17-dioxa-bicyclo[14.1.0]heptadec-11-yloxycarbonyloxymethyl]-2-nitro-phenyl ester (A) and

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-butanoic acid 4-(1R,3S,7S,10R,11S,12S,16S)-[10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yloxycarbonyloxymethyl]-phenyl ester (B)

32 mg (38µmol) of the compound prepared according to Example EL36 are reacted. After working-up and purification, 10.1 mg (12 µmol, 31%) of title compound A as well as 1.2 mg (1.4 µmol, 3,7%) of title compound B are isolated.

^{1}H-NMR ($CDCl_3$) of A: δ = 0.96 (3H), 1.04 (3H), 1.24 (3H), 1.29 (3H), 0.90-1.78 (7H), 2.04 (2H), 2.16 (2H), 2.20-2.62 (6H), 2.72 (1H), 2.84 (3H), 3.67 (2H), 3.69 (1H), 4.07 (1H), 4.20 (1H), 4.91 (1H), 4.95 (1H), 5.14 (2H), 5.22 (1H), 5.72 (1H), 6.24 (1H), 6.71 (2H), 7.10 (2H), 7.37 (1H), 7.40 (2H), 7.88 (1H), 7.97 (1H) ppm.

Example EL38

6-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-hexanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yloxycarbonyloxymethyl]-phenyl ester

Example EL38a

6-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-hexanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-4-(tert-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yloxycarbonyloxymethyl]-phenyl ester

Analogously to Example EL12b, 450 mg (640 µmol) of the compound prepared according to Example EL14a are reacted with 811 mg of the compound prepared according to Example L13. After working-up and purification, 108 mg (110 µmol, 17%) of the title compound are isolated.

Example EL38

6-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-hexanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yloxycarbonyloxymethyl]-phenyl ester

108mg (110 µmol) of the compound prepared according to Example EL38a in 22 ml dichloromethane are mixed with 1.06 ml (2.74 mmol) of a 20% solution of trifluoroacetic acid in dichloromethane. After 16 hours the mixture is diluted with dichloromethane and poured into a saturated solution of sodium bicarbonate. The mixture is extracted several times with dichloromethane and the combined organic extracts are dried over sodium sulfate. The residue obtained by filtration and removal of the solvent is purified by chromatography on fine silica gel. 64 mg (73 µmmol, 67%) of the title compound are isolated.

^{1}H-NMR ($CDCl_3$): δ = 1.02 (3H), 1.07 (3H), 1.16 (3H), 1.70 (3H), 0.98-1.96 (12H), 2.25-2.58 (8H), 2.83 (3H), 2.90 (2H), 3.55 (3H), 3.97 (1H), 4.92 (1H), 4.96 (1H), 5.15 (1H), 5.16 (2H), 5.22 (1H), 5.70 (1H), 5.82 (1H), 6.69 (2H), 7.08 (2H), 7.34 (1H), 7.41 (2H), 7.79 (1H), 7.94 (1H) ppm.

Example EL39

6-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-hexanoic acid 4-(1S,3S,7S,10R,11S,12S, 16R)-[10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yloxycarbonyloxymethyl]-phenyl ester (A) und 6-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-hexanoic acid 4-(1R,3S,7S,10R,11S,12S,16S)-[10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yloxycarbonyloxymethyl]-phenyl ester (B)

Analogously to Example EL2, 64 mg (73 µmol) of the compound prepared according to Example EL38 are reacted. After working-up and purification, 25 mg (28 µmol, 39%) of the title compound A as well as 5.4 mg (6.1 µmol, 8.3%) of the title compound B are isolated.

^{1}H-NMR ($CDCl_3$) of A: δ = 0.96 (3H), 1.04 (3H), 1.13-1.82 (13H), 1.23 (3H), 1.29 (3H), 2.15 (2H), 2.22-2.64 (6H), 2.71 (1H), 2.84 (3H), 3.54 (2H), 3.69 (1H), 4.08 (1H), 4.20 (1H), 4.91 (1H), 4.95 (1H), 5.14 (2H), 5.22 (1H), 5.72 (1H), 6.24 (1H), 6.69 (2H), 7.07 (2H), 7.37 (1H), 7.40 (2H), 7.82 (1H), 7.97 (1H) ppm.

Example EL40

11-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-undecanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yloxycarbonyloxymethyl]-phenyl ester

Example EL40a

11-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-undecanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-4-(tert-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yloxycarbonyloxymethyl]-phenyl ester

Analogously to Example EL12b, 450 mg (640 µmol) of the compound prepared according to Example EL14a are reacted with 992 mg of the compound prepared according to Example L14. After working-up and purification, 67 mg (63 µmol, 10%) of the title compound are isolated.

Example EL40

11-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-undecanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yloxycarbonyloxymethyl]-phenyl ester

Analogously to Example EL38, 67 mg (63 µmol) of the compound prepared according to Example EL40a are reacted. After working-up and purification, 23 mg (24 µmol, 38%) of the title compound are isolated.

^{1}H-NMR ($CDCl_3$): δ = 1.02 (3H), 1.07 (3H), 1.21 (3H), 1.70 (3H), 0.99-1.81 (21H), 1.91 (1H), 2.27-2.58 (8H), 2.83 (3H), 2.89 (2H), 3.50 (2H), 3.55 (1H), 3.97 (1H), 4.92 (1H), 4.96 (1H), 5.15 (1H), 5.16 (2H), 5.20 (1H), 5.70 (1H), 5.82 (1H), 6.68 (2H), 7.08 (2H), 7.34 (1H), 7.41 (2H), 7.79 (1H), 7.94 (1H) ppm.

Example EL41

11-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-undecanoic acid 4-(1S,3S,7S,10R,11S,12S,16R)-[10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yloxycarbonyloxymethyl]-phenyl ester (A) and 11-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-undecanoic acid 4-(1R,3S,7S,10R,11S,12S,16S)-[10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yloxycarbonyloxymethyl]-phenyl ester (B)

Analogously to Example EL2, 33 mg (35 µmol) of the compound prepared according to Example EL40 are reacted. After working-up and purification, 13 mg (14 µmol,

38%) of the title compound A as well as 4 mg (4 μmol, 12%) of the title compound B are isolated.

^{1}H-NMR ($CDCl_3$) of A: δ = 0.96 (3H), 1.04 (3H), 1.23 (3H), 0.91-1.78 (27H), 2.16 (2H), 2.23-2.68 (5H), 2.71 (1H), 2.84 (3H), 3.50 (2H), 3.69 (1H), 4.07 (1H), 4.20 (1H), 4.91 (1H), 4.95 (1H), 5.14 (2H), 5.22 (1H), 5.72 (1H), 6.24 (1H), 6.68 (2H), 7.07 (2H), 7.37 (1H), 7.40 (2H), 7.82 (1H), 7.97 (1H) ppm.

Example EL42

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-butanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-2-chlor-phenyl ester

Example EL42a

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-butanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-8-(tert-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-2-chlor-phenyl ester

Analogously to Example EL12b, 329 mg (467μmol) of the compound prepared according to Example EL12a are reacted with 885 mg of the compound prepared according to Example L15. After working-up and purification, 126 mg (127 μmol, 27%) of the title compound are isolated.

Example EL42

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-butanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-2-chlor-phenyl ester

Analogously to Example EL1, 126 mg (127 μmol) of the compound prepared according to Example EL42a are reacted. After working-up and purification, 79 mg (90 μmol, 71%) of the title compound are isolated.

^{1}H-NMR ($CDCl_3$): δ = 1.01 (3H), 1.13 (3H), 1.14 (3H), 1.70 (3H), 1.31-1.72 (17H), 2.75 (3H), 2.99 (1H), 3.40 (1H), 3.68 (3H), 4.49 (1H), 4.70 (1H), 5.00 (1H), 5.05 (1H), 5.18 (1H), 5.55 (1H), 5.71 (1H), 5.98 (1H), 6.72 (2H), 6.99 (1H), 7.07 (1H), 7.10 (1H), 7.36 (1H), 7.75 (1H), 7.95 (1H) ppm.

Example EL43

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-butanoic acid 4-(1S,3S,7S,10R,11S,12S, 16R)-[10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yloxycarbonyloxymethyl]-2-chlor-phenyl ester (A) and 4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-butanoic acid 4-(1R,3S,7S,10R,11S,12S, 16S)-[10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yloxycarbonyloxymethyl]-2-chlor-phenyl ester (B)

Analogously to Example EL2, 66 mg (75 µmol) of the compound prepared according to Example EL42 are reacted. After working-up and purification, 29.4 mg (32.9µmol, 44%) of the title compound A as well as 9.7 mg (10.9 µmol, 14%) of the title compound B are isolated.

^{1}H-NMR ($CDCl_3$) of A: δ = 1.03 (3H), 1.13 (3H), 1.15 (3H), 1.23 (1H), 1.31 (3H), 1.34-2.74 (17H), 2.78 (3H), 2.86 (1H), 3.44 (1H), 3.67 (3H), 4.46 (1H), 4.67 (1H), 5.01 (1H), 5.05 (1H), 5.46 (1H), 5.70 (1H), 6.08 (1H), 6.72 (2H), 7.01 (1H), 7.08 (1H), 7.16 (1H), 7.31 (1H), 7.77 (1H), 7.92 (1H) ppm.

Example EL44

6-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-hexanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-2-chloro-phenyl ester

Example EL44a

6-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-hexanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-8-(tert-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-2-chloro-phenyl ester

Analogously to Example EL12b, 329 mg (467 µmol) of the compound prepared according to Example EL12a are reacted with 821 mg of the compound prepared according to Example L16. After working-up and purification, 120 mg (118 µmol, 25%) of the title compound are isolated.

Example EL44

6-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-hexanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-2-chloro-phenyl ester

Analogously to Example EL1, 120 mg (118 µmol) of the compound prepared according to Example EL44a are reacted. After working-up and purification, 60 mg (66 µmol, 56%) of the title compound are isolated.

^{1}H-NMR ($CDCl_3$): δ = 1.01 (3H), 1.05 (1H), 1.13 (3H), 1.14 (3H), 1.33-1.89 (12H), 1.71 (3H), 2.24-2.70 (8H), 2.74 (3H), 3.00 (1H), 3.40 (1H), 3.55 (2H), 3.69 (1H), 4.49 (1H), 4.71 (1H), 5.00 (1H), 5.05 (1H), 5.18 (1H), 5.56 (1H), 5.71 (1H), 5.99 (1H), 6.70 (2H), 6.95 (1H), 7.03 (1H), 7.11 (1H), 7.37 (1H), 7.75 (1H), 7.95 (1H), ppm.

Example EL45

6-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-hexanoic acid 4-(1S,3S,7S,10R,11S,12S, 16R)-[10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yloxycarbonyloxymethyl]-2-chloro-phenyl ester (A) and 6-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-hexanoic acid 4-(1R,3S,7S,10R,11S,12S, 16S)-[10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yloxycarbonyloxymethyl]-2-chloro-phenyl ester (B)

Analogously to Example EL2, 60 mg (66 µmol) of the compound prepared according to Example EL44 is reacted. After working-up and purification, 32 mg (34.7 µmol, 53%) of the title compound A as well as 11 mg (11.9 µmol, 18%) of the title compound B are isolated.

^{1}H-NMR ($CDCl_3$) von A: δ = 1.02 (3H), 1.14 (3H), 1.15 (3H), 1.24 (1H), 1.32 (3H), 1.34-2.74 (21H), 2.77 (3H), 2.86 (1H), 3.44 (1H), 3.55 (2H), 3.69 (1H), 4.46 (1H), 4.67 (1H), 5.01 (1H), 5.05 (1H), 5.46 (1H), 5.70 (1H), 6.09 (1H), 6.69 (2H), 6.99 (1H), 7.04 (1H), 7.16 (1H), 7.32 (1H), 7.77 (1H), 7.92 (1H) ppm.

Example EL46

11-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-undecanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-2-chloro-phenyl ester

Example EL46a

11-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-undecanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-8-(tert-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-2-chloro-phenyl ester

Analogously to Example EL12b, 323 mg (459 µmol) of the compound prepared according to Example EL12a are reacted with 790 mg of the compound prepared according to Example L17. After working-up and purification, 96 mg (88 µmol, 19%) of the title compound are isolated.

Example EL46

11-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-undecanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-2-chlor-phenyl ester

Analogously to Example EL1, 59 mg (54 µmol) of the compound prepared according to Example EL46a are reacted. After working-up and purification, 27 mg (27.7 µmol, 51%) of the title compound are isolated.

^{1}H-NMR ($CDCl_3$): δ = 1.01 (3H), 1.13 (3H), 1.15 (3H), 1.23-2.70 (31H), 1.71 (3H), 2.74 (3H), 2.99 (1H), 3.40 (1H), 3.51 (2H), 3.68 (1H), 4.49 (1H), 4.70 (1H), 5.00 (1H), 5.04 (1H), 5.18 (1H), 5.56 (1H), 5.71 (1H), 5.99 (1H), 6.68 (2H), 6.95 (1H), 7.03 (1H), 7.11 (1H), 7.36 (1H), 7.75 (1H), 7.95 (1H) ppm.

Example EL47

11-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-undecanoic acid 4-(1S,3S,7S,10R,11S,12S,16R)-[10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yloxycarbonyloxymethyl]-2-chloro-phenyl ester (A) and 11-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-undecanoic acid 4-(1R,3S,7S,10R,11S,12S,16S)-[10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yloxycarbonyloxymethyl]-2-chloro-phenyl ester (B)

Analogously to Example EL2, 27 mg (27 µmol) of the compound prepared according to Example EL46 are reacted. After working-up and purification, 14 mg (14.1 µmol,

52%) of the title compound A as well as 5 mg (5.0 μmol, 19%) of the title compound B are isolated.

^{1}H-NMR ($CDCl_3$) of A: δ = 1.02 (3H), 1.13 (3H), 1.15 (3H), 1.19-1.84 (27H), 2.09-2.74 (8H), 2.77 (3H), 2.85 (1H), 3.44 (1H), 3.50 (2H), 3.69 (1H), 4.46 (1H), 4.67 (1H), 5.01 (1H), 5.06 (1H), 5.45 (1H), 5.70 (1H), 6.08 (1H), 6.68 (2H), 6.99 (1H), 7.04 (1H), 7.16 (1H), 7.31 (1H), 7.76 (1H), 7.91 (1H) ppm.

Example EL48

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-butanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yloxycarbonyloxymethyl]-2-chloro-phenyl ester

Example EL48a

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-butanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-4-(tert-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yloxycarbonyloxymethyl]-2-chloro-phenyl ester

Analogously to Example EL12b, 340 mg (482 μmol) of the compound prepared according to Example EL14a are reacted with 885 mg of the compound prepared according to Example L15. After working-up and purification, 151 mg (152 μmol, 32%) of the title compound are isolated.

Example EL48

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-butanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yloxycarbonyloxymethyl]-2-chloro-phenyl ester

Analogously to Example EL1, 151 mg (152 μmol) of the compound prepared according to Example EL48a are reacted. After working-up and purification, 46 mg (52 μmol, 34%) of the title compound are isolated.

^{1}H-NMR ($CDCl_3$): δ = 1.02 (3H), 1.07 (3H), 1.26 (3H), 1.71 (3H), 1.15-2.44 (13H), 2.51 (2H), 2.65 (2H), 2.84 (3H), 2.91 (1H), 3.55 (1H), 3.68 (2H), 3.99 (1H), 4.92 (1H), 4.98 (1H), 5.06-5.25 (4H), 5.70 (1H), 5.83 (1H), 6.72 (2H), 7.17 (1H), 7.31 (1H), 7.34 (1H), 7.49 (1H), 7.80 (1H), 7.96 (1H) ppm.

Example EL49

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-butanoic acid 4-(1S,3S,7S,10R,11S,12S, 16R)-[10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yloxycarbonyloxymethyl]-2-chloro-phenyl ester (A) and 4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-butanoic acid 4-(1R,3S,7S,10R,11S,12S,16S)-[10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yloxycarbonyloxymethyl]-2-chloro-phenyl ester (B)

Analogously to Example EL2, 46 mg (52 µmol) of the compound prepared according to Example EL48 are reacted. After working-up and purification, 6 mg (6.7 µmol, 13%) of the title compound A as well as 1 mg (1.1 µmol, 2%) of the title compound B are isolated.

^{1}H-NMR ($CDCl_3$) of A: δ = 0.97 (3H), 1.04 (3H), 1.24 (3H), 1.30 (3H), 1.14-2.76 (21H), 2.85 (3H), 3.68 (3H), 4.09 (1H), 4.23 (1H), 4.91 (1H), 4.97 (1H), 5.11 (2H), 5.22 (1H), 5.72 (1H), 6.25 (1H), 6.72 (2H), 7.16 (1H), 7.30 (1H), 7.37 (1H), 7.48 (1H), 7.83 (1H), 7.99 (1H) ppm.

Example EL50

6-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-hexanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yloxycarbonyloxymethyl]-2-chloro-phenyl ester

Example EL50a

6-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-hexanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-4-(tert-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yloxycarbonyloxymethyl]-2-chloro-phenyl ester

Analogously to Example EL12b, 340 mg (482 µmol) of the compound prepared according to Example EL14a are reacted with 848 mg of the compound prepared according to Example L16. After working-up and purification, 158 mg (155 µmol, 32%) of the title compound are isolated.

Example EL50

6-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-hexanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yloxycarbonyloxymethyl]-2-chloro-phenyl ester

Analogously to Example EL1, 158 mg (155 µmol) of the compound prepared according to Example EL50a are reacted. After working-up and purification, 58 mg (64 µmol, 41%) of the title compound are isolated.

^{1}H-NMR ($CDCl_3$): δ = 1.02 (3H), 1.08 (3H), 1.22 (3H), 1.71 (3H), 0.90-2.45 (17H), 2.51 (2H), 2.61 (2H), 2.83 (3H), 2.88 (1H), 3.55 (3H), 3.97 (1H), 4.92 (1H), 4.98 (1H), 5.10-5.25 (4H), 5.71 (1H), 5.83 (1H), 6.69 (2H), 7.12 (1H), 7.30 (1H), 7.34 (1H), 7.49 (1H), 7.79 (1H), 7.95 (1H) ppm.

Example EL51

6-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-hexanoic acid 4-(1S,3S,7S,10R,11S,12S, 16R)-[10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yloxycarbonyloxymethyl]-2-chloro-phenyl ester (A) and 6-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-hexanoic acid 4-(1R,3S,7S,10R,11S,12S,16S)-[10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yloxycarbonyloxymethyl]-2-chloro-phenyl ester (B)

Analogously to Example EL2, 58 mg (64 µmol) of the compound prepared according to Example EL50 are reacted. After working-up and purification, 25 mg (27 µmol, 42%) of the title compound A as well as 7 mg (7.6 µmol, 12%) of the title compound B are isolated.

^{1}H-NMR ($CDCl_3$) of A: δ = 0.97 (3H), 1.04 (3H), 1.24 (3H), 1.31 (3H), 1.12-2.65 (21H), 2.72 (1H), 2.84 (3H), 3.55 (2H), 3.71 (1H), 4.08 (1H), 4.22 (1H), 4.91 (1H), 4.96 (1H), 5.12 (2H), 5.23 (1H), 5.72 (1H), 6.24 (1H), 6.69 (2H), 7.13 (1H), 7.30 (1H), 7.37 (1H), 7.48 (1H), 7.83 (1H), 7.97 (1H) ppm.

Example EL52

11-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-undecanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yloxycarbonyloxymethyl]-2-chloro-phenyl ester

Example EL52a

11-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-undecanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-4-(tert-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yloxycarbonyloxymethyl]-2-chloro-phenyl ester

Analogously to Example EL12b, 355 mg (476 µmol) of the compound prepared according to Example EL14a are reacted with 790 mg of the compound prepared according to Example L17. After working-up and purification, 122 mg (112 µmol, 24%) of the title compound are isolated.

Example EL52

11-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-undecanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yloxycarbonyloxymethyl]-2-chloro-phenyl ester

Analogously to Example EL1, 122 mg (112 µmol) of the compound prepared according to Example EL52a are reacted. After working-up and purification, 28 mg (29 µmol, 26%) of the title compound are isolated.

^{1}H-NMR ($CDCl_3$): δ = 1.02 (3H), 1.08 (3H), 1.22 (3H), 1.11-2.48 (26H), 1.71 (3H), 2.51 (2H), 2.61 (2H), 2.83 (3H), 2.89 (1H), 3.46-3.58 (3H), 3.98 (1H), 4.61 (2H), 4.92 (1H), 4.98 (1H), 5.11-5.25 (3H), 5.70 (1H), 5.83 (1H), 6.68 (2H), 7.00 (1H), 7.18 (1H), 7.29 (1H), 7.36 (1H), 7.79 (1H), 7.95 (1H) ppm.

Example EL53

11-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-undecanoic acid 4-(1S,3S,7S,10R,11S,12S,16R)-[10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yloxycarbonyloxymethyl]-2-chloro-phenyl ester (A) and 11-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-undecanoic acid 4-(1R,3S,7S,10R,11S,12S,16S)-[10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yloxycarbonyloxymethyl]-2-chloro-phenyl ester (B)

Analogously to Example EL2, 28 mg (29 µmol) of the compound prepared according to Example EL52 are reacted. After working-up and purification, 6.2 mg (6.3 µmol,

22%) of the title compound A as well as 0.3 mg (0.3 μmol, 1%) of the title compound B are isolated.

^{1}H-NMR ($CDCl_3$) of A: δ = 0.97 (3H), 1.04 (3H), 1.23 (3H), 0.82-1.83 (25H), 2.16 (2H), 2.24-2.65 (7H), 2.72 (1H), 2.84 (3H), 3.50 (2H), 3.70 (1H), 4.08 (1H), 4.21 (1H), 4.92 (1H), 4.97 (1H), 5.11 (2H), 5.22 (1H), 5.72 (1H), 6.25 (1H), 6.67 (2H), 7.12 (1H), 7.30 (1H), 7.37 (1H), 7.49 (1H), 7.83 (1H), 7.98 (1H) ppm.

Example EL54

(4S,7R,8S,9S,13Z,16S)-Carbonic acid 7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yl ester 4-[4-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-3-nitro-butyrylamino]-benzyl ester

Example EL54a

(4S,7R,8S,9S,13Z,16S)-Carbonic acid 7-allyl-8-(tert-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yl ester 4-amino-benzyl ester

Analogously to Example EL12b, 160 mg (227 μmol) of the compound prepared according to Example EL12a are reacted with 191 mg (4-amino-3-nitro-phenyl)-methanol. After working-up and purification, 51 mg (61 μmol, 27%) of the title compound are isolated.

^{1}H-NMR ($CDCl_3$): δ = 0.07 (3H), 0.12 (3H), 0.92 (9H), 0.99 (3H), 1.03 (3H), 1.23 (3H), 0.85-1.74 (8H), 1.93 (1H), 2.28 (1H), 2.38 (2H), 2.49 (1H), 2.66 (1H), 2.77 (3H), 2.82 (1H), 2.97 (1H), 3.22 (1H), 3.87 (1H), 4.85-5.03 (4H), 5.22 (1H), 5.42 (1H), 5.74 (1H), 5.89 (1H), 6.10 (2H), 6.68 (1H), 7.19 (1H), 7.32 (1H), 7.73 (1H), 7.90 (1H), 7.98 (1H) ppm.

Example EL54b

(4S,7R,8S,9S,13Z,16S)-Carbonic acid 7-allyl-8-(tert-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yl ester 4-[4-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-butyrylamino]-3-nitro-benzyl ester

153 mg (837 μmol) of the compound prepared according to Example L4 are mixed with 1.82 ml thionyl chloride and refluxed for 3.5 hours. The mixture is diluted with

toluene and evaporated. A solution of 130 mg (156 µmol) of the compound prepared according to Example 54a in 6 ml dichloromethane is added, 75 µl pyridine are admixed, and the mixture is stirred at 23°C for 16 hours. It is poured into water, extracted several times with dichloromethane, the combined organic extracts are washed with water and dried over sodium sulfate. After filtration and removal of the solvent, the residue is purified by chromatography. 101 mg (101 µmol, 65%) of the title compound are isolated.

Example EL54

(4S,7R,8S,9S,13Z,16S)-Carbonic acid 7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yl ester 4-[4-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-butyrylamino]-3-nitro-benzyl ester

Analogously to Example EL1, 101 mg (101 µmol) of the compound prepared according to Example EL54a are reacted. After working-up and purification, 62 mg (70 µmol, 69%) of the title compound are isolated.

^{1}H-NMR ($CDCl_3$): δ = 1.01 (3H), 1.14 (6H), 1.39 (2H), 1.64 (2H), 1.71 (3H), 1.80 (2H), 2.07 (2H), 2.23-2.54 (8H), 2.69 (1H), 2.77 (3H), 2.96 (1H), 3.39 (1H), 3.65 (2H), 3.69 (1H), 4.52 (1H), 4.75 (1H), 5.00 (1H), 5.05 (1H), 5.18 (1H), 5.55 (1H), 5.71 (1H), 5.98 (1H), 6.71 (2H), 7.31 (1H), 7.36 (1H), 7.77 (1H), 7.91 (1H), 7.93 (1H), 8.67 (1H), 10.28 (1H) ppm.

Example EL55

(1S,3S,7S,10R,11S,12S,16R)-Carbonic acid 10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yl ester 4-[4-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-butyrylamino]-3-nitro-benzyl ester (A) and (1R,3S,7S,10R,11S,12S,16S)-Carbonic acid 10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yl ester 4-[4-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-butyrylamino]-3-nitro-benzyl ester (B)

Analogously to Example EL2, 62 mg (70 µmol) of the compound prepared according to Example EL54 are reacted. After working-up and purification, 38 mg (42 µmol, 60%) of the title compound A as well as 11 mg (12 µmol, 17%) of the title compound B are isolated.

^{1}H-NMR ($CDCl_3$) of A: δ = 1.03 (3H), 1.13 (3H), 1.17 (3H), 1.32 (3H), 1.20-2.58 (17H), 2.70 (1H), 2.79 (3H), 2.85 (1H), 3.43 (1H), 3.65 (2H), 3.69 (1H), 4.52 (1H), 4.72 (1H), 5.01 (1H), 5.05 (1H), 5.45 (1H), 5.70 (1H), 6.07 (1H), 6.71 (2H), 7.31 (1H), 7.35 (1H), 7.78 (1H), 7.88 (1H), 7.95 (1H), 8.68 (1H), 10.28 (1H) ppm.

Example EL56

(4S,7R,8S,9S,13Z,16S)-Carbonic acid 7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yl ester 4-[6-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-hexanoylamino]-3-nitro-benzyl ester

Example EL56a

(4S,7R,8S,9S,13Z,16S)-Carbonic acid 7-allyl-8-(tert-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yl ester 4-[6-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-hexanoylamino]-3-nitro-benzyl ester

Analogously to Example EL54b, 50 mg (60 μmol) of the compound prepared according to Example EL54a are reacted with the compound prepared according to Example L5. After working-up and purification, 58 mg (56 μmol, 94%) of the title compound are isolated.

Example EL56

(4S,7R,8S,9S,13Z,16S)-Carbonic acid 7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yl ester 4-[6-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-hexanoylamino]-3-nitro-benzyl ester

Analogously to Example EL1, 82 mg (80 μmol) of the compound prepared according to Example EL56a are reacted. After working-up and purification, 34 mg (37 μmol, 46%) of the title compound are isolated.

^{1}H-NMR ($CDCl_3$): δ = 1.01 (3H), 1.14 (6H), 1.70 (3H), 1.31-2.57 (20H), 2.69 (1H), 2.78 (3H), 2.97 (1H), 3.39 (1H), 3.54 (2H), 3.69 (1H), 4.51 (1H), 4.74 (1H), 5.00 (1H), 5.05 (1H), 5.18 (1H), 5.55 (1H), 5.78 (1H), 5.98 (1H), 6.69 (2H), 7.31 (1H), 7.36 (1H), 7.76 (1H), 7.92 (1H), 7.93 (1H), 8.71 (1H), 10.32 (1H) ppm.

Example EL57

(1S,3S,7S,10R,11S,12S,16R)-Carbonic acid 10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yl ester 4-[6-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-hexanoylamino]-3-nitro-benzyl ester (A) and (1R,3S,7S,10R,11S,12S,16S)-Carbonic acid 10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yl ester 4-[6-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-hexanoylamino]-3-nitro-benzyl ester (B)

Analogously to Example EL2, 34 mg (37 µmol) of the compound prepared according to Example EL56 are reacted. After working-up and purification, 19 mg (20.4 µmol, 55%) of the title compound A as well as 6 mg (6.4 µmol, 17%) of the title compound B are isolated.

^{1}H-NMR ($CDCl_3$) of A: δ = 1.02 (3H), 1.14 (3H), 1.15 (3H), 1.39 (2H), 1.70 (3H), 1.65 (2H), 1.80 (2H), 2.06 (2H), 2.23-2.55 (8H), 2.69 (1H), 2.77 (3H), 2.97 (1H), 3.39 (1H), 3.65 (2H), 3.69 (1H), 4.52 (1H), 4.75 (1H), 5.00 (1H), 5.05 (1H), 5.18 (1H), 5.55 (1H), 5.71 (1H), 5.97 (1H), 6.71 (2H), 7.31 (1H), 7.36 (1H), 7.76 (1H), 7.91 (1H), 7.93 (1H), 8.68 (1H), 10.28 (1H) ppm.

Example EL58

(4S,7R,8S,9S,13Z,16S)-Carbonic acid 7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yl ester 4-[11-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-undecanoylamino]-3-nitro-benzyl ester

Example EL58a

(4S,7R,8S,9S,13Z,16S)-Carbonic acid 7-allyl-8-(tert-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yl ester 4-[11-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-undecanoylamino]-3-nitro-benzyl ester

Analogously to Example EL54b, 130 mg (156 µmol) of the compound prepared according to Example EL54a are reacted with the compound prepared according to Example L6. After working-up and purification, 120 mg (109 µmol, 70%) of the title compound are isolated.

Example EL58

(4S,7R,8S,9S,13Z,16S)-Carbonic acid 7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yl ester 4-[11-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-undecanoylamino]-3-nitro-benzyl ester

Analogously to Example EL1, 120 mg (109 µmol) of the compound prepared according to Example EL58a are reacted. After working-up and purification, 89 mg (90 µmol, 83%) of the title compound are isolated.

^{1}H-NMR ($CDCl_3$): δ = 1.01 (3H), 1.13 (3H), 1.14 (3H), 1.70 (3H), 1.04-2.56 (30H), 2.69 (1H), 2.78 (3H), 2.97 (1H), 3.39 (1H), 3.50 (2H), 3.69 (1H), 4.52 (1H), 4.74 (1H), 5.01 (1H), 5.05 (1H), 5.18 (1H), 5.55 (1H), 5.71 (1H), 5.97 (1H), 6.67 (2H), 7.31 (1H), 7.36 (1H), 7.76 (1H), 7.91 (1H), 7.93 (1H), 8.72 (1H), 10.33 (1H) ppm.

Example EL59

(1S,3S,7S,10R,11S,12S,16R)-Carbonic acid 10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yl ester 4-[11-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-undecanoylamino]-3-nitro-benzyl ester (A) and (1R,3S,7S,10R,11S,12S,16S)-Carbonic acid 10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yl ester 4-[11-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-undecanoylamino]-3-nitro-benzyl ester (B)

Analogously to Example EL2, 89 mg (90 µmol) of the compound prepared according to Example EL58 are reacted. After working-up and purification, 45 mg (µmol, %) of the title compound A as well as 15 mg (µmol, %) of the title compound B are isolated.

^{1}H-NMR ($CDCl_3$) of A: δ = 1.03 (3H), 1.13 (3H), 1.16 (3H), 1.20-1.83 (26H), 2.09-2.57 (8H), 2.72 (1H), 2.79 (3H), 2.86 (1H), 3.44 (1H), 3.50 (2H), 3.69 (1H), 4.51 (1H), 4.72 (1H), 5.01 (1H), 5.05 (1H), 5.45 (1H), 5.71 (1H), 6.08 (1H), 6.68 (2H), 7.32 (1H), 7.35 (1H), 7.78 (1H), 7.88 (1H), 7.96 (1H), 8.73 (1H), 10.33 (1H) ppm.

Example EL60

(4S,7R,8S,9S,13Z,16S)-Carbonic acid 7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yl ester 6-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-hexyl ester

Example EL60a

(4S,7R,8S,9S,13Z,16S)-Carbonic acid 7-allyl-8-(tert-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yl ester 6-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-hexyl ester

Analogously to Example EL12b, 1.25 g (1.77 mmol) of the compound prepared according to Example EL12a are reacted with 1.75 g of the compound prepared according to L18. After working-up and purification, 119 mg (138 µmol, 8%) of the title compound are isolated.

Example EL60

(4S,7R,8S,9S,13Z,16S)-Carbonic acid 7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yl ester 6-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-hexyl ester

Analogously to Example EL1, 101 mg (117 µmol) of the compound prepared according to Example EL60a are reacted. After working-up and purification, 68 mg (91 µmol, 77%) of the title compound are isolated.

^{1}H-NMR ($CDCl_3$): δ = 1.02 (3H), 1.12-1.87 (19H), 1.70 (3H), 2.23-2.56 (6H), 2.66 (1H), 2.83 (3H), 2.97 (1H), 3.40 (2H), 3.48 (2H), 3.68 (1H), 3.75 (1H), 5.01 (1H), 5.05 (1H), 5.17 (2H), 5.51 (1H), 5.72 (1H), 5.97 (1H), 6.68 (2H), 7.35 (1H), 7.78 (1H), 7.92 (1H) ppm.

Example EL61

(1S,3S,7S,10R,11S,12S,16R)-Carbonic acid 10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yl ester 6-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-hexyl ester (A) and (1R,3S,7S,10R,11S,12S,16S)-Carbonic acid 10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yl ester 6-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-hexyl ester (B)

Analogously to Example EL2, 68 mg (91 µmol) of the compound prepared according to Example EL60 are reacted. After working-up and purification, 26 mg (34 µmol, 37%) of the title compound A as well as 10 mg (13 µmol, 14%) of the title compound B are isolated.

^{1}H-NMR ($CDCl_3$) of A: δ = 1.03 (3H), 1.14 (3H), 1.18 (3H), 1.32 (3H), 1.10-1.85 (15H), 2.11-2.43 (5H), 2.52 (1H), 2.70 (1H), 2.84 (3H), 2.86 (1H), 3.38-3.51 (4H), 3.69 (1H), 3.74 (1H), 5.01 (1H), 5.05 (1H), 5.42 (1H), 5.72 (1H), 6.07 (1H), 6.69 (2H), 7.32 (1H), 7.80 (1H), 7.90 (1H) ppm.

Example EL62

(4S,7R,8S,9S,13Z,16S)-Carbonic acid 7-allyl-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yl ester 4-[4-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-3-nitro-butyrylamino]-benzyl ester

Example EL62a

(4S,7R,8S,9S,13Z,16S)-Carbonic acid 7-allyl-4-(tert-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yl ester 4-amino-benzyl ester

Analogously to Example EL12b, 1.73 g (2.46 mmol) of the compound prepared according to Example EL14a are reacted with 2.06 g (4-amino-3-nitro-phenyl)-methanol. After working-up and purification, 420 mg (502 µmol, 20%) of the title compound are isolated.

^{1}H-NMR ($CDCl_3$): δ = -0.10 (3H), 0.09 (3H), 0.84 (9H), 0.96-1.21 (2H), 1.01 (3H), 1.12 (3H), 1.15 (3H), 1.70 (3H), 1.61-1.85 (4H), 2.11 (1H), 2.29 (2H), 2.54-2.78 (3H), 2.83 (3H), 2.90 (1H), 3.31 (1H), 3.93 (1H), 4.86 (1H), 4.96 (1H), 5.04 (1H), 5.11 (1H), 5.25 (2H), 5.55 (1H), 5.72 (1H), 6.14 (2H), 6.82 (1H), 7.35 (1H), 7.43 (1H), 7.79 (1H), 7.91 (1H), 8.18 (1H) ppm.

Example EL62b

(4S,7R,8S,9S,13Z,16S)-Carbonic acid 7-allyl-4-(tert-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yl ester 4-[4-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-butyrylamino]-3-nitro-benzyl ester

Analogously to Example EL54b, 140 mg (167 µmol) of the compound prepared according to Example EL62a are reacted with the compound prepared according to Example L4. After working-up and purification, 150 mg (150 µmol, 90%) of the title compound are isolated.

Example EL62

(4S,7R,8S,9S,13Z,16S)-Carbonic acid 7-allyl-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yl ester 4-[4-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-3-nitro-butyrylamino]-benzyl ester

Analogously to Example EL1, 145 mg (145 μmol) of the compound prepared according to Example EL62a are reacted. After working-up and purification, 67 mg (76 μmol, 52%) of the title compound are isolated.

^{1}H-NMR ($CDCl_3$): δ = 1.02 (3H), 1.08 (3H), 1.22 (3H), 1.70 (3H), 1.09-2.12 (8H), 2.27-2.55 (8H), 2.83 (3H), 2.87 (2H), 3.56 (1H), 3.65 (2H), 3.99 (1H), 4.93 (1H), 4.98 (1H), 5.12-5.26 (4H), 5.71 (1H), 5.83 (1H), 6.70 (2H), 7.33 (1H), 7.67 (1H), 7.79 (1H), 7.94 (1H), 8.25 (1H), 8.79 (1H), 10.32 (1H) ppm.

Example EL63

(1S,3S,7S,10R,11S,12S,16R)-Carbonic acid 10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yl ester 4-[4-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-butyrylamino]-3-nitro-benzyl ester (A) and (1R,3S,7S,10R,11S,12S,16S)-Carbonic acid 10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yl ester 4-[4-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-butyrylamino]-3-nitro-benzyl ester (B)

Analogously to Example EL2, 67 mg (76 μmol) of the compound prepared according to Example EL62 are reacted. After working-up and purification, 37 mg (41 μmol, 54%) of the title compound A as well as 12 mg (13 μmol, 18%) of the title compound B are isolated.

Example EL64

(4S,7R,8S,9S,13Z,16S)-Carbonic acid 7-allyl-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yl ester 4-[4-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-3-nitro-hexanoylamino]-benzyl ester

Example EL64a

(4S,7R,8S,9S,13Z,16S)-Carbonic acid 7-allyl-4-(tert-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yl ester 4-[4-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)- hexanoylamino]-3-nitro-benzyl ester

Analogously to Example EL54b, 140 mg (167 µmol) of the compound prepared according to Example EL62a are reacted with the compound prepared according to Example L5. After working-up and purification, 155 mg (150 µmol, 90%) of the title compound are isolated.

Example EL64

(4S,7R,8S,9S,13Z,16S)-Carbonic acid 7-allyl-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yl ester 4-[4-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-3-nitro-hexanoylamino]-benzyl ester

Analogously to Example EL1, 150 mg (151µmol) of the compound prepared according to Example EL64a are reacted. After working-up and purification, 68 mg (74 µmol, 49%) of the title compound are isolated.

^{1}H-NMR ($CDCl_3$): δ = 1.02 (3H), 1.07 (3H), 1.23 (3H), 1.70 (3H), 1.16-2.54 (20H), 2.84 (3H), 2.87 (2H), 3.54 (3H), 3.98 (1H), 4.92 (1H), 4.98 (1H), 5.13-5.26 (4H), 5.71 (1H), 5.83 (1H), 6.68 (2H), 7.33 (1H), 7.67 (1H), 7.79 (1H), 7.94 (1H), 8.26 (1H), 8.82 (1H), 10.37 (1H) ppm.58

Example EL65

(1S,3S,7S,10R,11S,12S,16R)-Carbonic acid 10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yl ester 4-[4-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)- hexanoylamino]-3-nitro-benzyl ester (A) and (1R,3S,7S,10R,11S,12S,16S)-Carbonic acid 10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yl ester 4-[4-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-hexanoylamino]-3-nitro-benzyl ester (B)

Analogously to Example EL2, 68 mg (74 µmol) of the compound prepared according to Example EL64 are reacted. After working-up and purification, 44 mg (47 µmol, 64%) of the title compound A as well as 3 mg (3 µmol, 4%) of the title compound B are isolated.

Example EL66

(4S,7R,8S,9S,13Z,16S)-Carbonic acid 7-allyl-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yl ester 4-[4-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-3-nitro-undecanoylamino]-benzyl ester

Example EL66a

(4S,7R,8S,9S,13Z,16S)-Carbonic acid 7-allyl-4-(tert-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yl ester 4-[4-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)- undecanoylamino]-3-nitro-benzyl ester

Analogously to Example EL54b, 140 mg (167 µmol) of the compound prepared according to Example EL62a are reacted with the compound prepared according to Example L6. After working-up and purification, 165 mg (150 µmol, 90%) of the title compound are isolated.

Example EL66

(4S,7R,8S,9S,13Z,16S)-Carbonic acid 7-allyl-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yl ester 4-[4-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-3-nitro-undecanoylamino]-benzyl ester

Analogously to Example EL1, 145 mg (132 µmol) of the compound prepared according to Example EL66a are reacted. After working-up and purification, 106 mg (108 µmol, 82%) of the title compound are isolated.

^{1}H-NMR ($CDCl_3$): δ = 1.01 (3H), 1.06 (3H), 1.24 (3H), 1.70 (3H), 1.14-2.57 (30H), 2.82 (3H), 2.89 (2H), 3.50 (2H), 3.55 (1H), 4.01 (1H), 4.92 (1H), 4.99 (1H), 5.11-5.28 (4H), 5.70 (1H), 5.83 (1H), 6.69 (2H), 7.34 (1H), 7.67 (1H), 7.79 (1H), 7.96 (1H), 8.26 (1H), 8.85 (1H), 10.38 (1H) ppm.

Example EL67

(1S,3S,7S,10R,11S,12S,16R)-Carbonic acid 10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yl ester 4-[4-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)- undecanoylamino]-3-nitro-benzyl ester (A) and (1R,3S,7S,10R,11S,12S,16S)-Carbonic acid 10-allyl-7-hydroxy-8,8,12,16-

tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yl ester 4-[4-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-undecanoylamino]-3-nitro-benzyl ester (B)

Analogously to Example EL2, 106 mg (108 µmol) of the compound prepared according to Example EL66 are reacted. After working-up and purification, 58 mg (58 µmol, 54%) of the title compound A as well as 6 mg (6 µmol, 6%) of the title compound B are isolated.

^{1}H-NMR ($CDCl_3$) of A: δ = 0.96 (3H), 1.04 (3H), 1.23 (3H), 1.31 (3H), 0.81-1.83 (23H), 2.16 (2H), 2.23-2.66 (6H), 2.71 (1H), 2.85 (3H), 3.5 (2H), 3.72 (1H), 4.08 (1H), 4.24 (1H), 4.92 (1H), 4.97 (1H), 5.15 (2H), 5.22 (1H), 5.72 (1H), 6.25 (1H), 6.68 (2H), 7.36 (1H), 7.66 (1H), 7.83 (1H), 7.97 (1H), 8.25 (1H), 8.83 (1H), 10.37 (1H) ppm.

Examples of the Synthesis of Effector-Linker Recognition Units (ELE)

Example ELE1

[3-(3-(AP39r)-Sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-propyl]-carbamic acid-10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yl ester

Example ELE1a

Reduction of an Antibody Fragment with Terminal Cysteine

A single-strand protein that consists of the variable domains of the heavy and light antibody chains (single-chain Fv, scFv) of the amino acid sequence EVQLLESGGGLVQPGGSLRLSCAASGFTFSSFSMSWVRQAPGKGLEWVSSISG SSGTTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKPFPYFDY WGQGTLVTVSSGDGSSGGSGGASEIVLTQSPGTLSLSPGERATLSCRASQSVSS SFLAWYQQKPGQAPRLLIYYASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAV YYCQQTGRIPPTFGQGTKVEIKGGGCA, which specifically recognizes the fibronectin domain B (ED-B) and is referred to as AP39, is used for coupling after reduction of the c-terminal cysteine.

For reduction, the solution of 661 µg of tri(2-carboxyethyl)phosphine-hydrochloride in 236 µl of PBS is mixed with the solution of 1.54 mg of AP39 in 1.12 ml of PBS, and it is incubated for 1.5 hours at 25°C. Desalination is done with a pre-equilibrated NAP-5 column at a concentration of 450 µl of AP39r and 50 µl of PBS. After elution with 1 ml of PBS, the reduced antibody fragment AP39r is isolated in a concentration of 0.7 mg/ml.

Example ELE1

(1S,3S,7S(3RS),10R,11S,12S,16R)-[3-(3-(AP39r)-Sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-propyl]-carbamic acid-10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yl ester

22.5 µl of a 1.38 mmol solution of effector-linker conjugate A in DMSO, prepared according to Example EL2, is added to 400 µl of the solution, prepared according to Example ELE1a, of the reduced antibody fragment, mixed with 77.5 µl of PBS and incubated at 25°C for 1 hour. Desalination is done with a pre-equilibrated

NAP5 column at a concentration of 500 µl of the reaction solution. After elution with PBS, the solution of the title compound is isolated The dilution factor relative to the antibody fragment is approximately 2.5.

m/z (Calc.): 26203.1 m/z (exp.): 26218 ± 20

Example ELE2

(1S,3S,7S(3RS),10R,11S,12S,16R)-[5-(3-(AP39r)-Sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-pentyl]-carbamic acid-10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadec-7-yl ester

Analogously to Example ELE1, the antibody fragment that is reduced according to Example ELE1a is reacted with effector-linker conjugate A that is prepared according to Example EL4, and the solution of the title compound is isolated. The dilution factor relative to the antibody fragment is approximately 2.5.

m/z (Calc.): 26231.2 m/z (exp.): 26236 ± 20

Example ELE3

(1S,3S,7S(3RS),10R,11S,12S,16R)-[10-(3-(AP39r)-Sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-decyl]-carbamic acid-10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadec-7-yl ester

Analogously to Example ELE1, the antibody fragment that is reduced according to Example ELE1a is reacted with effector-linker conjugate A that is prepared according to Example EL6, and the solution of the title compound is isolated. The dilution factor relative to the antibody fragment is approximately 2.5.

m/z (Calc.): 26301.4 m/z (exp.): 26303 ± 20

Example ELE4

(1S,3S,7S,10R,11S(3RS),12S,16R)-[3-(3-(AP39r)-Sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-propyl]-carbamic acid-10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadec-11-yl ester

Analogously to Example ELE1, the antibody fragment that is reduced according to Example ELE1a is reacted with effector-linker conjugate A that is prepared according to Example EL8, and the solution of the title compound is isolated. The dilution factor relative to the antibody fragment is approximately 2.5.

m/z (Calc.): 26203.2 m/z (exp.): 26206 ± 20

Example ELE5

(1S,3S,7S,10R,11S(3RS),12S,16R)-[5-(3-(AP39r)-Sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-pentyl]-carbamic acid-10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadec-11-yl ester

Analogously to Example ELE1, the antibody fragment that is reduced according to Example ELE1a is reacted with effector-linker conjugate A that is prepared according to Example EL10, and the solution of the title compound is isolated. The dilution factor relative to the antibody fragment is approximately 2.5.

m/z (Calc.): 26231.2 m/z (exp.): 26225 ± 20

Example ELE6

(1S,3S(E),7S,10R,11S,12S,16R)-[3-(3-(AP39r)-Sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-propyl]-carbamic acid-7-[3-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-propylcarbamoyloxy]-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-thiazol-4-yl)-vinyl]-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yl ester (A) and

(1S,3S(E),7S,10R,11S,12S,16R)-[3-(3-(AP39r)-Sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-propyl]-carbamic acid-11-[3-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-propylcarbamoyloxy]-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-thiazol-4-yl)-vinyl]-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yl ester (B)

Analogously to Example ELE1, the antibody fragment that is reduced according to Example ELE1a is reacted with the effector-linker conjugate that is prepared according to Example EL11, and the solution of the title compounds is isolated. The dilution factor relative to the antibody fragment is approximately 2.5.

m/z (Calc.): 26347.3 m/z (exp.): 26358 ± 20

Example ELE7

(1S,3S(E),7S,10R,11S,12S,16R)-*N*-[1-({4-[2-(7,11-Dihydroxy-8,8,10,12,16-pentamethyl-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-3-yl)-propenyl]-thiazol-2-ylmethyl}-carbamoyl)-ethyl]-3-(AP39r)-disulfanyl-*N*-methyl-propionamide

Analogously to Example ELE1, the antibody fragment that is reduced according to Example ELE1a is reacted with effector-linker conjugate A that is

prepared according to Example EL16, and the solution of the title compound is isolated. The dilution factor relative to the antibody fragment is approximately 2.5.

m/z (Calc.): 26173 m/z (exp.): 26174 ± 20

Example ELE8

(1S,3S(E),7S,10R,11S,12S,16R)-2-[Methyl-(3-(AP39r)-disulfanyl-propionyl)-amino]-propionic acid-4-[2-(7,11-dihydroxy-8,8,10,12,16-pentamethyl-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-3-yl)-propenyl]-thiazol-2-ylmethyl ester

Analogously to Example ELE1, the antibody fragment that is reduced according to Example ELE1a is reacted with effector-linker conjugate A that is prepared according to Example EL17, and the solution of the title compound is isolated. The dilution factor relative to the antibody fragment is approximately 2.5.

m/z (Calc.): 26174 m/z (exp.): 26163 ± 20

Example ELE9

(1S,3S,7S,10R,11S,12S,16R)-Carbonic acid-10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yl ester 4-(3-(AP39r)-sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-phenyl ester

Analogously to Example ELE1, the antibody fragment that is reduced according to Example ELE1a is reacted with effector-linker conjugate A that is prepared according to Example EL13, and the solution of the title compound is isolated. The dilution factor relative to the antibody fragment is approximately 2.5.

m/z (Calc.): 26238 m/z (exp.): 26224 ± 20

Example ELE10

(1S,3S,7S,10R,11S,12S,16R)-Carbonic acid-10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yl ester 4-(3-(AP39r)-sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-phenyl ester

Analogously to Example ELE1, the antibody fragment that is reduced according to Example ELE1a is reacted with effector-linker conjugate A that is prepared according to Example EL15, and the solution of the title compound is isolated. The dilution factor relative to the antibody fragment is approximately 2.5.

m/z (Calc.): 26238 m/z (exp.): 26243 ± 20

Example ELE11

4-(3-(AP39r)-Sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-butanoic acid 4-(1S,3S,7S,10R,11S, 12S,16R)-[10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

Analogously to Example ELE1, the antibody fragment that is reduced according to Example ELE1a is reacted with effector-linker conjugate A that is prepared according to Example EL19, and the solution of the title compound is isolated. The dilution factor relative to the antibody fragment is approximately 2.5.

m/z (Calc.): 26383 m/z (exp.): 26377 ± 20

Example ELE12

4-(3-(AP39r)-Sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-butanoic acid 4-(1S,3S,7S,10R,11S,12S,16R)-[10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

Analogously to Example ELE1, the antibody fragment that is reduced according to Example ELE1a is reacted with effector-linker conjugate A that is prepared according to Example EL25, and the solution of the title compound is isolated. The dilution factor relative to the antibody fragment is approximately 2.5.

m/z (Calc.): 26383 m/z (exp.): 26381 ± 20

Example ELE13

6-(3-(AP39r)-sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-hexanoic acid 4-(1S,3S,7S,10R,11S,12S, 16R)-[10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

Analogously to Example ELE1, the antibody fragment that is reduced according to Example ELE1a is reacted with the effector-linker conjugate A that is prepared

according to Example EL21, and the solution of the title compound is isolated. The dilution factor relative to the antibody fragment is approximately 2.5.

m/z (Calc.) : 26411 m/z (exp.): 26384 ± 30

m/z (Calc.) : 25673 m/z (exp.): 25657 ± 20 (6-(3-(AP39r)-sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-hexanoic acid fragment)

Example ELE14

11-(3-(AP39r)-sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-undecanoic acid 4-(1S,3S,7S,10R,11S,12S, 16R)-[10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

Analogously to Example ELE1, the antibody fragment that is reduced according to Example ELE1a is reacted with the effector-linker conjugate A that is prepared according to Example EL23 and the solution of the title compound is isolated. The dilution factor relative to the antibody fragment is approximately 2.5.

m/z (Calc.) : 26482 m/z (exp.): 26477 ± 20

m/z (Calc.) : 25744 m/z (exp.): 26752 ± 20 (11-(3-(AP39r)-sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-undecanoic acid fragment)

Example ELE15

6-(3-(AP39r)-sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-hexanoic acid 4-(1S,3S,7S,10R,11S,12S, 16R)-[10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

Analogously to Example ELE1, the antibody fragment that is reduced according to Example ELE1a is reacted with the effector-linker conjugate A that is prepared according to Example EL27 and the solution of the title compound is isolated. The dilution factor relative to the antibody fragment is approximately 2.5.

m/z (Calc.) : 26411 m/z (exp.): 26398 ± 20

m/z (Calc.) : 25673 m/z (exp.): 25665 ± 20 (6-(3-(AP39r)-sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-hexanoic acid fragment)

Example ELE16

11-(3-(AP39r)-sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-undecanoic acid 4-(1S,3S,7S,10R,11S,12S, 16R)-[10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

Analogously to Example ELE1, the antibody fragment that is reduced according to Example ELE1a is reacted with the effector-linker conjugate A that is prepared according to Example EL29 and the solution of the title compound is isolated. The dilution factor relative to the antibody fragment is approximately 2.5.

m/z (Calc.) : 26482 m/z (exp.): 26491 ± 20

m/z (Calc.) : 25744 m/z (exp.): 25757 ± 20 (11-(3-(AP39r)-sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-undecanoic acid fragment)

Example ELE17

4-(3-(AP39r)-sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-butanoic acid 4-(1S,3S,7S,10R,11S,12S, 16R)-[10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yloxycarbonyloxymethyl]-phenyl ester

Analogously to Example ELE1, the antibody fragment that is reduced according to Example ELE1a is reacted with the effector-linker conjugate A that is prepared according to Example EL31 and the solution of the title compound is isolated. The dilution factor relative to the antibody fragment is approximately 2.5.

m/z (Calc.) : 26338 m/z (exp.): 26304 ± 30

Example ELE18

6-(3-(AP39r)-sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-hexanoic acid 4-(1S,3S,7S,10R,11S,12S, 16R)-[10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yloxycarbonyloxymethyl]-phenyl ester

Analogously to Example ELE1, the antibody fragment that is reduced according to Example ELE1a is reacted with the effector-linker conjugate A that is prepared according to Example EL33 and the solution of the title compound is isolated. The dilution factor relative to the antibody fragment is approximately 2.5.

m/z (Calc.) : 26366 m/z (exp.): 26347 ± 30

Example ELE19

11-(3-(AP39r)-sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-undecanoic acid 4-(1S,3S,7S,10R,11S,12S, 16R)-[10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yloxycarbonyloxymethyl]-phenyl ester

Analogously to Example ELE1, the antibody fragment that is reduced according to Example ELE1a is reacted with the effector-linker conjugate A that is prepared according to Example EL35 and the solution of the title compound is isolated. The dilution factor relative to the antibody fragment is approximately 2.5.

m/z (Calc.) : 26437 m/z (exp.): 26412 ± 30

Example ELE20

4-(3-(AP39r)-sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-butanoic acid 4-(1S,3S,7S,10R,11S,12S, 16R)-[10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

Analogously to Example ELE1, the antibody fragment that is reduced according to Example ELE1a is reacted with the effector-linker conjugate A that is prepared according to Example EL37 and the solution of the title compound is isolated. The dilution factor relative to the antibody fragment is approximately 2.5.

m/z (Calc.) : 26338 m/z (exp.): 26338 ± 20

Example ELE21

6-(3-(AP39r)-sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-hexanoic acid 4-(1S,3S,7S,10R,11S,12S, 16R)-[10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yloxycarbonyloxymethyl]-phenyl ester

Analogously to Example ELE1, the antibody fragment that is reduced according to Example ELE1a is reacted with the effector-linker conjugate A that is prepared according to Example EL39 and the solution of the title compound is isolated. The dilution factor relative to the antibody fragment is approximately 2.5.

m/z (Calc.) : 26366 m/z (exp.): 26384 ± 30

Example ELE22

11-(3-(AP39r)-sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-undecanoic acid 4-(1S,3S,7S,10R,11S,12S, 16R)-[10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yloxycarbonyloxymethyl]-phenyl ester

Analogously to Example ELE1, the antibody fragment that is reduced according to Example ELE1a is reacted with the effector-linker conjugate A that is prepared according to Example EL41 and the solution of the title compound is isolated. The dilution factor relative to the antibody fragment is approximately 2.5.

m/z (Calc.) : 26437 m/z (exp.): 26421 ± 30

Example ELE23

4-(3-(AP39r)-sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-butanoic acid 4-(1S,3S,7S,10R,11S,12S, 16R)-[10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yloxycarbonyloxymethyl]-2-chloro-phenyl ester

Analogously to Example ELE1, the antibody fragment that is reduced according to Example ELE1a is reacted with the effector-linker conjugate A that is prepared according to Example EL43 and the solution of the title compound is isolated. The dilution factor relative to the antibody fragment is approximately 2.5.

m/z (Calc.) : 26373 m/z (exp.): 26358 ± 20

m/z (Calc.) : 25645 m/z (exp.): 25627 ± 20 (4-(3-(AP39r)-sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-butanoic acid fragment)

Example ELE24

6-(3-(AP39r)-sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-hexanoic acid 4-(1S,3S,7S,10R,11S,12S, 16R)-[10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yloxycarbonyloxymethyl]-2-chloro-phenyl ester

Analogously to Example ELE1, the antibody fragment that is reduced according to Example ELE1a is reacted with the effector-linker conjugate A that is prepared

according to Example EL45 and the solution of the title compound is isolated. The dilution factor relative to the antibody fragment is approximately 2.5.
m/z (Calc.) : 26401 m/z (exp.): 26395 ± 20

Example ELE25
11-(3-(AP39r)-sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-undecanoic acid 4-(1S,3S,7S,10R,11S,12S, 16R)-[10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yloxycarbonyloxymethyl]-2-chlor-phenyl ester
Analogously to Example ELE1, the antibody fragment that is reduced according to Example ELE1a is reacted with the effector-linker conjugate A that is prepared according to Example EL47 and the solution of the title compound is isolated. The dilution factor relative to the antibody fragment is approximately 2.5.
m/z (Calc.) : 26471 m/z (exp.): 26463 ± 20

Example ELE26
4-(3-(AP39r)-sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-butanoic acid 4-(1S,3S,7S,10R,11S,12S, 16R)-[10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yloxycarbonyloxymethyl]-2-chloro-phenyl ester
Analogously to Example ELE1, the antibody fragment that is reduced according to Example ELE1a is reacted with the effector-linker conjugate A that is prepared according to Example EL49 and the solution of the title compound is isolated. The dilution factor relative to the antibody fragment is approximately 2.5.
m/z (Calc.) : 26373 m/z (exp.): 26341 ± 30

Example ELE27
6-(3-(AP39r)-sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-hexanoic acid 4-(1S,3S,7S,10R,11S,12S, 16R)-[10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yloxycarbonyloxymethyl]-2-chlor-phenyl ester
Analogously to Example ELE1, the antibody fragment that is reduced according to Example ELE1a is reacted with the effector-linker conjugate A that is prepared

according to Example EL51 and the solution of the title compound is isolated. The dilution factor relative to the antibody fragment is approximately 2.5.
m/z (Calc.) : 26401 m/z (exp.): 26391 ± 20

Example ELE28
11-(3-(AP39r)-sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-undecanoic acid 4-(1S,3S,7S,10R,11S,12S, 16R)-[10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yloxycarbonyloxymethyl]-2-chlor-phenyl ester
Analogously to Example ELE1, the antibody fragment that is reduced according to Example ELE1a is reacted with the effector-linker conjugate A that is prepared according to Example EL53 and the solution of the title compound is isolated. The dilution factor relative to the antibody fragment is approximately 2.5.
m/z (Calc.) : 26471 m/z (exp.): 26466 ± 20

Example ELE29
(1S,3S,7S,10R,11S,12S,16R)-Carbonic acid 10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yl ester 4-[4-(3-(AP39r)-sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-butyrylamino]-3-nitro-benzyl ester
Analogously to Example ELE1, the antibody fragment that is reduced according to Example ELE1a is reacted with the effector-linker conjugate A that is prepared according to Example EL55 and the solution of the title compound is isolated. The dilution factor relative to the antibody fragment is approximately 2.5.
m/z (Calc.) : 26337 m/z (exp.): ± 20

Example ELE30
(1S,3S,7S,10R,11S,12S,16R)-Carbonic acid 10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yl ester 4-[6-(3-(AP39r)-sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-hexanoylamino]-3-nitro-benzyl ester
Analogously to Example ELE1, the antibody fragment that is reduced according to Example ELE1a is reacted with the effector-linker conjugate A that is prepared

according to Example EL57 and the solution of the title compound is isolated. The dilution factor relative to the antibody fragment is approximately 2.5.
m/z (Calc.) : 26365 m/z (exp.): ± 20

Example ELE31
(1S,3S,7S,10R,11S,12S,16R)-Carbonic acid 10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yl ester 4-[11-(3-(AP39r)-sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-undecanoylamino]-3-nitro-benzyl ester
Analogously to Example ELE1, the antibody fragment that is reduced according to Example ELE1a is reacted with the effector-linker conjugate A that is prepared according to Example EL59 and the solution of the title compound is isolated. The dilution factor relative to the antibody fragment is approximately 2.5.
m/z (Calc.) : 26436 m/z (exp.): ± 20

Example ELE32
(1S,3S,7S,10R,11S,12S,16R)-Carbonic acid 10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yl ester 6-(3-(AP39r)-sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-hexyl ester
Analogously to Example ELE1, the antibody fragment that is reduced according to Example ELE1a is reacted with the effector-linker conjugate A that is prepared according to Example EL61 and the solution of the title compound is isolated. The dilution factor relative to the antibody fragment is approximately 2.5.
m/z (Calc.) : 26246 m/z (exp.): ± 20

Example ELE33
4-(3-(2H8-Ab)x-sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-butanoic acid 4-(1S,3S,7S,10R,11S,12S, 16R)-[10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yloxycarbonyloxymethyl]-2-nitro-phenyl ester
100 µl of a solution of the thionylated antibody prepared according to Example ELE33a (about 3 nmol, about 6 thiol groups) are mixed with 42.3 µl of a 1.1 mM

solution of the effector-linker conjugate A prepared according to Example EL25 in PBS, and the mixture is incubated at 23°C for 1 hour. Desalination is performed by using a pre-equilibrated NAP5 column with a loading of 150 µl of the reaction solution. After elution with PBS, the solution of the title compound is isolated. The loading factor x of antibody 2H8-A in relation to effector-linker is about 1:4 to 1:5.

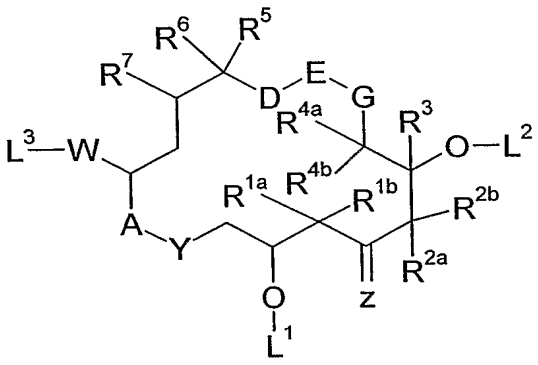
Example ELE33a

Thionylation of a complete immunoglobuline (IgG), e.g., the 2H8 antibody

For the introduction of thionyl groups an amine-free solution of the 2H8 antibody in phosphate buffer having a concentration in the range of about 1-10 mg/ml at a pH of 7.2 is mixed with the 10- to 100-fold excess of 2-iminothiolane and is allowed to react for 1 hour at 23 °C. The number of the introduced thiol groups is 1 to about 15 depending on the excess of reagent.

Claims:

1. Effector conjugate of general formula (I):



I,

in which

R^{1a}, R^{1b}, independently of one another, are hydrogen, C_1-C_{10} alkyl, aryl, aralkyl, or together a $-(CH_2)_m$ group, in which m is 2 to 5,

R^{2a}, R^{2b}, independently of one another, are hydrogen, C_1-C_{10} alkyl, aryl, aralkyl, or together a $-(CH_2)_n$ group, in which n is 2 to 5, or C_2-C_{10} alkenyl, or C_2-C_{10} alkynyl,

R^3 is hydrogen, C_1-C_{10} alkyl, aryl or aralkyl, and

R^{4a}, R^{4b}, independently of one another, are hydrogen, C_1-C_{10} alkyl, aryl, aralkyl, or together a $-(CH_2)_p$ group, in which p is 2 to 5,

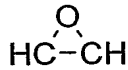
R^5 is hydrogen, C_1-C_{10} alkyl, aryl, aralkyl, CO_2H, CO_2alkyl, CH_2OH, CH_2Oalkyl, CH_2Oacyl, CN, CH_2NH_2, CH_2N(alkyl, acyl)$_{1,2}$, or CH_2Hal,

Hal is a halogen atom,

R^6, R^7 in each case are hydrogen, or together an additional bond, or together an

oxygen atom, or together an NH group, or together an N-alkyl group, or together a CH_2 group, and

G is an oxygen atom or CH_2,

D-E is a group H_2C-CH_2, HC=CH, C≡C, CH(OH)-CH(OH), CH(OH)-CH_2, CH_2-CH(OH),  , O-CH_2, or, if G represents a CH_2 group, D-E is

CH_2-O,

W is a group C(=X)R^8, or a bicyclic or tricyclic aromatic or heteroaromatic radical,

L^3 is hydrogen, or, if a radical in W contains a hydroxyl group, forms a group O-L^4 with the latter, or, if a radical in W contains an amino group, forms a group NR^{25}-L^4 with the latter,

R^{25} is hydrogen or C_1-C_{10} alkyl,

X is an oxygen atom, or two OR^{20} groups, or a C_2-C_{10} alkylenedioxy group that may be straight or branched, or H/OR^9, or a $CR^{10}R^{11}$ group,

R^8 is hydrogen, C_1-C_{10} alkyl, aryl, aralkyl, halogen or CN, and

R^9 is hydrogen or a protective group PG^X,

R^{10}, R^{11}, in each case independently of one another, are hydrogen, C_1-C_{20} alkyl, aryl, aralkyl, or together with a methylene carbon atom form a 5- to 7-membered carbocyclic ring,

Z can represent oxygen or H/OR^{12},

R^{12} can represent hydrogen or a protective group PG^Z,

A-Y can represent a group O-C(=O), O-CH_2, CH_2-C(=O), NR^{21}-C(=O) or NR^{21}-SO_2,

R^{20} can represent C_1-C_{20} alkyl,

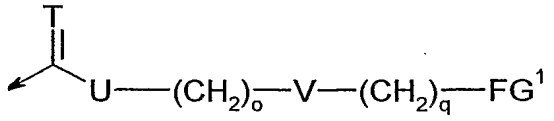
R^{21} can represent a hydrogen atom or C_1-C_{10} alkyl,

PG^X, PG^Y, and PG^Z can represent a protective group PG, and

L^1, L^2, and L^4, independently of one another, can represent hydrogen, a group C(=O)Cl, a group C(=S)Cl, a group PG^Y or a linker of general formula (III) or (IV);

provided that at least one substituent L^1, L^2 or L^4 represents a linker of general formula (III) or (IV);

the linker of general formula (III) has the following structure,



III,

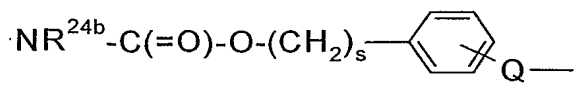
in which

T can represent oxygen or sulfur,

U can represent oxygen, CHR^{22}, CHR^{22}-NR^{23}-C(=O)-, O-C(=O)-CHR^{22}-NR^{23}-C(=O)-, O-C(=O)-CHR^{22}-NR^{23}-C(=S)-, CHR^{22}-NR^{23}-C(=S)- or NR^{24a},

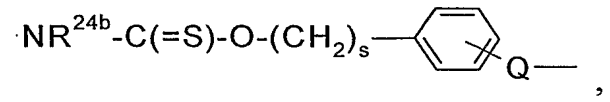
o can represent 0 to 15,

V can represent a bond, aryl, a group



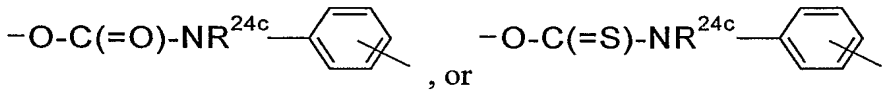
,

or a group



s can represent 0 to 4,

Q can represent a bond, O-C(=O)-NR^{24c}, O-C(=S)-NR^{24c},

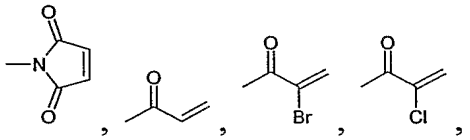


R^{22} can represent hydrogen, C_1-C_{10} alkyl, aryl or aralkyl,

R^{23} can represent hydrogen or C_1-C_{10} alkyl,

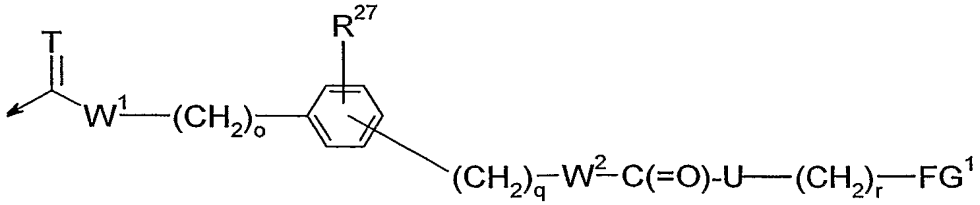
R^{24a}, R^{24b}, and R^{24c}, independently of one another, can represent hydrogen or C_1-C_{10} alkyl,

q can represent 0 to 15,

FG^1 can represent C_1-C_{10} alkyl-S_3, 

 , or CO_2H; and

the linker of general formula (IV) has the following structure,



IV,

in which

T can represent oxygen or sulfur,

W^1, W^2 are the same or different and can represent oxygen or NR^{24a},

o can represent 0 to 5,

R^{24a} can represent hydrogen or C_1-C_{10} alkyl,

R^{27} can represent halogen, CN, NO_2, CO_2R^{28}, or OR^{28},

R^{28} can represent hydrogen, C_1-C_{10} alkyl, aryl or aralkyl,

q can represent 0 to 5,

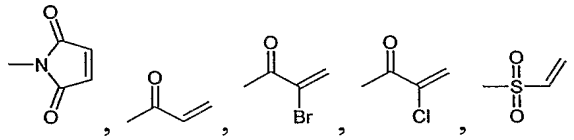
U can represent oxygen, CHR^{22}, CHR^{22}-NR^{23}-C(=O)-, CHR^{22}-NR^{23}-C(=S)- or C_1-C_{20} alkyl,

R^{22} can represent hydrogen, C_1-C_{10} alkyl, aryl or aralkyl,

R^{23} can represent hydrogen or C_1-C_{10} alkyl,

r can represent 0 to 20,

FG^1 can represent C_1-C_{10} alkyl-S_3,



, or CO_2H,

as a single isomer or a mixture of different isomers and/or as a pharmaceutically acceptable salt thereof.

2. Effector conjugate according to claim 1, wherein:

A-Y represents O-C(=O) or NR^{21}-C(=O),

D-E represents an H_2C-CH_2 group,

G represents a CH_2 group,

Z represents an oxygen atom,

R^{1a}, R^{1b} in each case represent C_1-C_{10} alkyl or together a $-(CH_2)_p$ group with p equal to 2 or 3 or 4,

R^{2a}, R^{2b}, independently of one another, represent hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, or C_2-C_{10} alkynyl,

R^3 represents hydrogen,

R^{4a}, R^{4b}, independently of one another, represent hydrogen or C_1-C_{10} alkyl;

R^5 represents hydrogen, or C_1-C_4 alkyl or CH_2OH or CH_2NH_2 or $CH_2N(alkyl, acyl)_{1,2}$ or CH_2Hal,

R^6 and R^7 together represent an additional bond or together an NH group, or together an N-alkyl group, or together a CH_2 group, or together an oxygen atom,

W represents a group $C(=X)R^8$ or a 2-methylbenzothiazol-5-yl radical or a 2-methylbenzoxazol-5-yl radical or a quinolin-7-yl radical or a 2-aminomethylbenzothiazol-5-yl radical or a 2-hydroxymethylbenzothiazol-5-yl radical or a 2-aminomethyl-benzoxazol-5-yl radical or a 2-hydroxymethylbenzoxazol-5-yl radical,

X represents a $CR^{10}R^{11}$ group,

R^8 represents hydrogen or C_1-C_4 alkyl or a fluorine atom or a chlorine atom or a bromine atom,

R^{10}/R^{11} represent hydrogen/2-methylthiazol-4-yl or hydrogen/2-pyridyl or hydrogen/2-methyloxazol-4-yl or hydrogen/2-aminomethylthiazol-4-yl or hydrogen/2-aminomethyloxazol-4-yl or hydrogen/2-hydroxymethylthiazol-4-yl or hydrogen/2-hydroxymethyloxazol-4-yl.

3. Effector conjugate according to claim 1 or 2, wherein the effector element is selected from the group that consists of:

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-1-methyl-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-16-[2-(2-Aminomethyl-thiazol-4-yl)-1-methyl-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-1-methyl-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-1-methyl-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-methyl-2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-1-methyl-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-16-[2-(2-Aminomethyl-thiazol-4-yl)-1-methyl-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-methyl-2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-1-methyl-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]hepta-decane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-1-methyl-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]hepta-decane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-fluoro-2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-1-fluoro-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-thiazol-4-yl)-1-fluoro-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-fluoro-2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-1-fluoro-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-1-fluoro-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-chloro-2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-1-chloro-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-thiazol-4-yl)-1-chloro-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-chloro-2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-1-chloro-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-1-chloro-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-fluoro-2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-1-fluoro-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-thiazol-4-yl)-1-fluoro-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-fluoro-2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-1-fluoro-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]hepta-decane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-1-fluoro-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]hepta-decane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-chloro-2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-1-chloro-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-thiazol-4-yl)-1-chloro-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-chloro-2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-1-chloro-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]hepta-decane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-1-chloro-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-methyl-2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-methyl-2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-fluoro-2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-fluoro-2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-chloro-2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-chloro-2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-fluoro-2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-fluoro-2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-chloro-2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-chloro-2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl-oxazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-oxazol-4-yl)-1-methyl-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-16-[2-(2-Aminomethyl-oxazol-4-yl)-1-methyl-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-oxazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-oxazol-4-yl)-1-methyl-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-oxazol-4-yl)-1-methyl-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-methyl-2-(2-methyl-oxazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-oxazol-4-yl)-1-methyl-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-16-[2-(2-Aminomethyl-oxazol-4-yl)-1-methyl-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-methyl-2-(2-methyl-oxazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-oxazol-4-yl)-1-methyl-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]hepta-decane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-oxazol-4-yl)-1-methyl-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]hepta-decane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-fluoro-2-(2-methyl-oxazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-oxazol-4-yl)-1-fluoro-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-oxazol-4-yl)-1-fluoro-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-fluoro-2-(2-methyl-oxazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-oxazol-4-yl)-1-fluoro-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-oxazol-4-yl)-1-fluoro-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-chloro-2-(2-methyl-oxazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-oxazol-4-yl)-1-chloro-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-oxazol-4-yl)-1-chloro-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-chloro-2-(2-methyl-oxazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-oxazol-4-yl)-1-chloro-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-oxazol-4-yl)-1-chloro-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-fluoro-2-(2-methyl-oxazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-oxazol-4-yl)-1-fluoro-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-oxazol-4-yl)-1-fluoro-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-fluoro-2-(2-methyl-oxazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-oxazol-4-yl)-1-fluoro-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]hepta-decane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-oxazol-4-yl)-1-fluoro-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]hepta-decane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-chloro-2-(2-methyl-oxazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-oxazol-4-yl)-1-chloro-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-oxazol-4-yl)-1-chloro-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-chloro-2-(2-methyl-oxazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-oxazol-4-yl)-1-chloro-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]hepta-decane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-oxazol-4-yl)-1-chloro-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]hepta-decane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-16-[2-(2-Aminomethyl-thiazol-4-yl)-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-16-[2-(2-Aminomethyl-thiazol-4-yl)-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-propyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-propyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-propyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-propyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-propyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-propyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-butyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-butyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-butyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-butyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-butyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-butyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-allyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-allyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-allyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-allyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-allyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-allyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-prop-2-inyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-prop-2-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-prop-2-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-prop-2-inyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-prop-2-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-prop-2-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-but-3-enyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-but-3-enyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-but-3-enyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-but-3-enyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-but-3-enyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-but-3-enyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-but-3-inyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-but-3-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-but-3-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-but-3-inyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-but-3-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-but-3-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-propyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-propyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-propyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-propyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-propyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-propyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-butyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-butyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-butyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-butyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-butyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-butyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-allyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-allyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-allyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-allyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-allyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-allyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-prop-2-inyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-prop-2-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-prop-2-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-prop-2-inyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-prop-2-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-prop-2-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-but-3-enyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-but-3-enyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-but-3-enyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-but-3-enyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-but-3-enyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-but-3-enyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-but-3-inyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-but-3-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-but-3-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-but-3-inyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-but-3-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-but-3-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

wherein the hydrogen atoms in the above-mentioned effector elements are replaced in the positions indicated in formula (I) by radicals L^1-L^3.

4. Effector conjugate according to any one of claims 1-3, wherein the linker is selected from the group that consists of the compounds of general formula (III), wherein

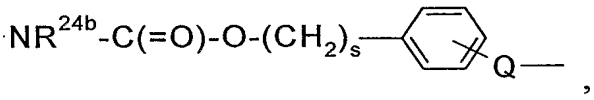
V represents a bond or an aryl radical,

o is zero, and

T is an oxygen atom.

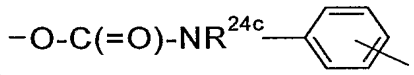
5. Effector conjugate according to any one of claims 1-3, wherein the linker is selected from the group that consists of the compounds of general formula (III), wherein

V represents a bond or an aryl radical or a group



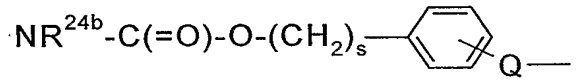
,

o is 0 to 4, and

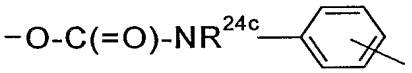
Q is a bond or a group  .

6. Effector conjugate according to claim 5, wherein

V is a bond or a group



,

Q is a bond or a group  ,

o is 0, 2 or 3,

s is 1, and

T is an oxygen atom.

7. Effector conjugate according to any one of claims 1-3, wherein the linker is selected from the group that consists of compounds of general formula (IV), wherein

o is 0 to 4, and

q is 0 to 3.

8. Effector conjugate according to claim 7, wherein

o is 0, 2 or 3,

W^1 is oxygen,

q is 0,

R^{22} is hydrogen, C_1-C_3 alkyl or aralkyl,

R^{23} is hydrogen or C_1-C_3 alkyl,

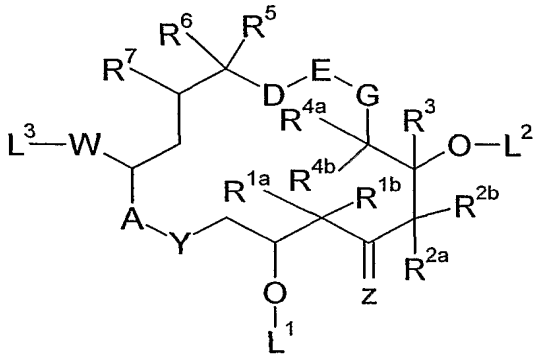
R^{24a} is hydrogen or C_1-C_3 alkyl,

R^{27} is fluorine, chlorine, CN, NO_2, CO_2R^{28} or OR^{28},

R^{28} is hydrogen or C_1-C_5 alkyl, and

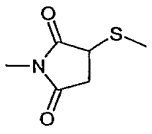
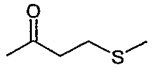
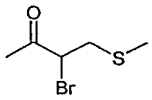
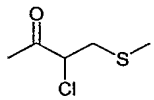
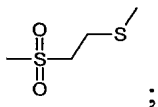
U is oxygen, CHR^{22}, or CHR^{22}-NR^{23}-C(=O)-.

9. Effector recognition unit conjugate of general formula (I),



I,

wherein the substituents therein have the meanings that are mentioned in claim 1, but at least one group FG^1 is replaced by a group FG^{2a} or FG^{2b}, wherein FG^{2a} or FG^{2b} can have the following meanings:

FG^{2a}: -S-S-,  ,  ,  ,  ,  ;

FG^{2b}: -CONH-;

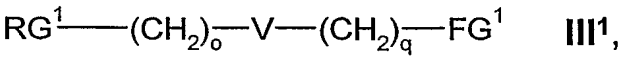
and wherein a recognition unit is conjugated via a sulfur atom with the group FG^{2a} or via an amide function with group FG^{2b}; wherein the recognition unit is selected from the group that consists of peptides, soluble receptors, cytokines, lymphokines, aptamers, spiegelmers, recombinant proteins, new framework structures, monoclonal antibodies and fragments of monoclonal antibodies;

as a single isomer or a mixture of different isomers and/or as a pharmaceutically acceptable salt thereof.

10. Effector recognition unit conjugate according to claim 9, wherein the conjugate contains more than one recognition unit, and wherein the recognition units are identical.

11. Effector recognition unit conjugate according to claim 9 or 10, wherein the recognition unit is an antibody, or an antigen-binding fragment thereof, which is specific for an antigen that is selected from the group that consists of the antigens that are cited in Table 1, as well as CD19, CD20, CD40, CD22, CD25, CD5, CD52, CD10, CD2, CD7, CD33, CD38, CD40, CD72, CD4, CD21, CD37, CD30, VCAM, CD31, ELAM, endoglin, VEGFRI/II, $\alpha_v\beta_3$, Tie1/2, TES23 (CD44ex6), phosphatidylserine, PSMA, VEGFR/VEGF complex and ED-B-fibronectin.

12. Linker of general formula (III^1):

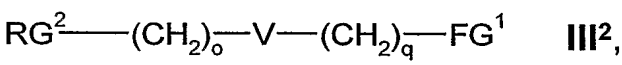


III^1,

in which

RG^1 is an O=C=N group or an S=C=N group, and o, V, q and FG^1 have the meanings that are mentioned in claim 1;

or linker of general formula (III^2):

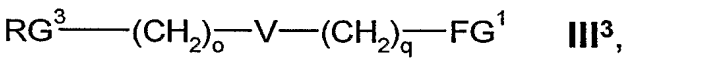


III^2,

in which

RG^2 is a Hal-C(=T)-CHR^{22} group, or a Hal-C(=T)-CHR^{22}-NR^{23}-C(=T) group, or an R^{26}-C(=O)-O-C(=T)-CHR^{22} group, or an R^{26}-C(=O)-O-C(=T)-CHR^{22}-NR^{23}-C(=T) group, wherein R^{26} is C_1-C_{10} alkyl, aryl, or aralkyl, and o, V, q and FG^1 have the meanings that are mentioned in claim 1;

or linker of general formula (III^3):



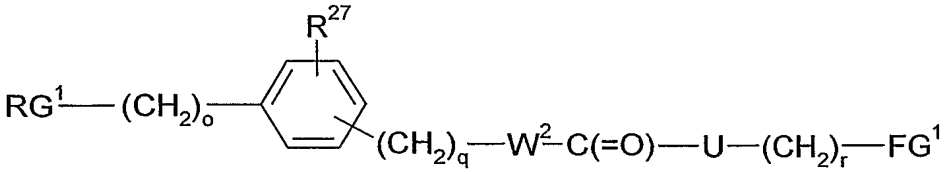
III^3,

in which

RG^3 is an OH group, or an NHR^{24a} group, or a COOH group, and o, V, q and FG^1 have the meanings that are mentioned in claim 1;

but with the proviso that the compound 1-(4-amino-phenyl)-pyrrole-2,5-dione is not included.

13. Linker of general formula (IV^1):



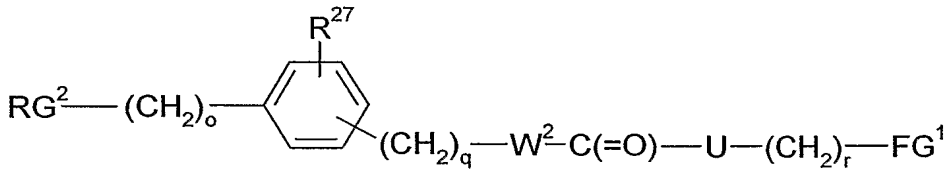
IV^1

,

in which

RG^1 is an O=C=N group or an S=C=N group, and o, q, r, W^2, R^{27}, U and FG^1 have the meanings that are mentioned in claim 1;

or linker of general formula (IV^2):



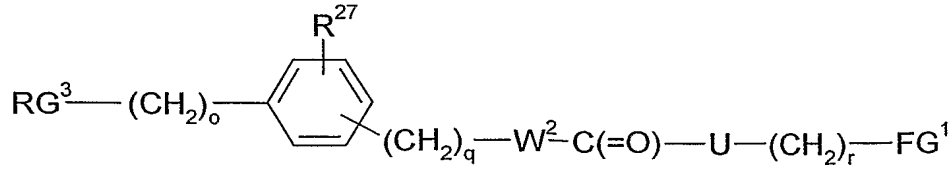
IV^2

,

in which

RG^2 is a Hal-C(=T)-CHR^{22} group, or a Hal-C(=T)-CHR^{22}-NR^{23}-C(=T) group, or an R^{26}-C(=O)-O-C(=T)-CHR^{22} group, or an R^{26}-C(=O)-O-C(=T)-CHR^{22}-NR^{23}-C(=T) group, wherein R^{26} is C_1-C_{10} alkyl, aryl, or aralkyl, and R^{22}, R^{23}, T, o, q, r, W^2, R^{27}, U and FG^1 have the meanings that are mentioned in claim 1;

or linker of general formula (IV^3):



IV^3

,

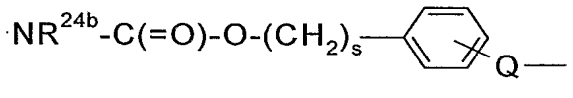
in which

RG^3 is an OH group or an NHR^{24a} group or a COOH group, and R^{24}, o, q, r, W^2, R^{27}, U and FG^1 have the meanings that are mentioned in claim 1.

14. Linker according to claim 12, wherein V represents a bond or an aryl radical, o is equal to zero, and T is an oxygen atom.

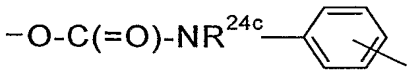
15. Linker according to claim 12, wherein

V represents a bond or an aryl radical or a group



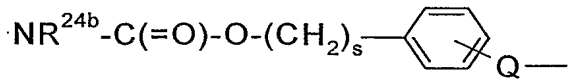
,

o is 0 to 4, and

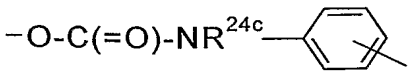
Q is a bond or a group  .

16. Linker according to claim 15, wherein

V is a bond or a group



,

Q is a bond or a group  ,

o is 0, 2 or 3,

s is 1, and

T is an oxygen atom.

17. Linker according to claim 13, wherein

o is 0 to 4, and

q is 0 to 3.

18. Linker according to claim 17, wherein

o is 0, 2 or 3,

W^1 is oxygen,

q is 0,

R^{22} is hydrogen, C_1-C_3 alkyl or aralkyl,

R^{23} is hydrogen or C_1-C_3 alkyl,

R^{24a} is hydrogen or C_1-C_3 alkyl,

R^{27} is fluorine, chlorine, CN, NO_2, CO_2R^{28} or OR^{28},

R^{28} is hydrogen, or C_1-C_5 alkyl, and

U is oxygen, CHR^{22}, or CHR^{22}-NR^{23}-C(=O)-.

19. Method for the production of effector conjugates according to any one of claims 1-8, wherein a compound of general formula (I), wherein the substituents have the meanings that are mentioned in claim 1, but the condition that at least one substituent L^1, L^2 or L^4 represent a linker of general formula (III) or (IV) need not be met, and at least one substituent L^1, L^2 or L^4 represents hydrogen, a group C(=O)Cl, or a group C(=S)Cl, is reacted with a linker that is selected from the group that consists of a linker of general formula (III^1), (III^2), (III^3), (IV^1), (IV^2) or (IV^3), as described in claims 12 to 18.

20. Method for the production of effector recognition unit conjugates according to one of claims 9 to 11, wherein an effector conjugate according to any one of claims 1-8 is reacted with at least one recognition unit as defined in claims 9 and 11.

21. Use of a compound of general formula (I), wherein the substituents have the meanings that are mentioned in claim 1, but the condition that at least one substituent L^1, L^2 or L^4 represent a linker of general formula (III) or (IV) need not be met, and at least one substituent L^1, L^2 or L^4 represents hydrogen, a group C(=O)Cl, or a group C(=S)Cl, in a method according to claim 19.

22. Use of a compound of general formula (I) for the production of an effector recognition unit conjugate according to claims 9 to 11.

23. Use of a linker of general formula (III^1), (III^2), (III^3), (IV^1), (IV^2) or (IV^3) in a method according to claim 19.

24. Use of a linker of general formula (III^1), (III^2), (III^3), (IV^1), (IV^2) or (IV^3) for the production of an effector recognition unit conjugate according to any one of claims 9 to 11.

25. Use of a recognition unit, as defined in claim 9 or 11, in a method according to claim 20.

26. Effector recognition unit conjugate according to any one of claims 9 to 11 for use as a medicament.

27. Effector recognition unit conjugate according to any one of claims 9 to 11 for use as a medicament for treating diseases that are associated with proliferative processes.

28. Effector recognition unit conjugate according to any one of claims 9 to 11 for use as a medicament for treating a disease that is selected from the group that consists of tumors, inflammatory diseases, neurodegenerative diseases, angiogenesis-associated diseases, multiple sclerosis, Alzheimer's disease, and rheumatoid arthritis.

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103 05 098.1	7 February 2003 (07.02.2003)	DE
60/451,673	5 March 2003 (05.03.2003)	US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:

— *as to the identity of the inventor (Rule 4.17(i)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

Published:

— *with international search report*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report: 27 May 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NEW EFFECTOR CONJUGATES, PROCESS FOR THEIR PRODUCTION AND THEIR PHARMACEUTICAL USE

(57) Abstract: Conjugates of epothilones and epothilone derivatives (as effectors) with suitable biomolecules (as recognition units) are described. Their production is carried out by the effectors being reacted with suitable linkers, and the compounds that are produced are conjugated to the recognition units. The pharmaceutical use of the conjugates for treating proliferative or angiogenesis-associated processes is described.

WO 2004/012735 A3

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/08483

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/427 C07D417/06 C07D493/04 C07D207/40 C07C323/24
A61K47/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, EMBASE, CHEM ABS Data, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BERSUKER I B ET AL: "Improved electron-conformational method of pharmacophore identification and bioactivity prediction. Application to angiotensin converting enzyme inhibitors." JOURNAL OF CHEMICAL INFORMATION AND COMPUTER SCIENCES. 2000 NOV-DEC, vol. 40, no. 6, November 2000 (2000-11), pages 1363-1376, XP002274169 ISSN: 0095-2338 figure 4	12
X	EP 0 121 350 A (SMITHKLINE BECKMAN CORP) 10 October 1984 (1984-10-10) examples	12

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 March 2004	05/04/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Skjöldebrand, C

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/08483

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 03/005026 A (AMERSHAM BIOSCIENCES UK LTD ; OSBORN NIGEL JOHN (GB); SWEET ALISON CLA) 16 January 2003 (2003-01-16) examples	13
P,X	WANG LAI-XI ET AL: "Carbohydrate-centered maleimide cluster as a new type of templates for multivalent peptide assembling: Synthesis of multivalent HIV-1 gp41 peptides." BIOORGANIC AND MEDICINAL CHEMISTRY, vol. 11, no. 1, 2 January 2003 (2003-01-02), pages 159-166, XP002274170 & ISSN: 0968-0896 abstract	13
X	REGHUNADHAN NAIR C P ET AL: "Free radical copolymerisation of N-(4-hydroxy phenyl) maleimide with vinyl monomers: Solvent and penultimate-unit effects" EUROPEAN POLYMER JOURNAL, PERGAMON PRESS LTD. OXFORD, GB, vol. 35, no. 10, 28 July 1999 (1999-07-28), pages 1829-1840, XP004179475 ISSN: 0014-3057 abstract	13
X	KALGUTKAR A S ET AL: "Inactivation of prostaglandin endoperoxide synthase (PGHS) by N-(substituted)maleimides." ADVANCES IN EXPERIMENTAL MEDICINE AND BIOLOGY. 1997, vol. 407, 1997, pages 79-85, XP0009027572 ISSN: 0065-2598 the whole document	13
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/08483

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01/64650 A (SLOAN KETTERING INST CANCER ; CHAPPELL MARK (US); STACHEL SHAWN (US);) 7 September 2001 (2001-09-07) page 9 - page 10 figure 9	1-28
A	WO 01/92255 A (KOSAN BIOSCIENCES INC ; ASHLEY GARY (US); FARDIS MARIA (US); SANTI DAN) 6 December 2001 (2001-12-06) page 37 - page 38 examples 33,34	1-28
A	US 2002/058286 A1 (WU ZHICAI ET AL) 16 May 2002 (2002-05-16) the whole document	1-28
A	WO 01/83800 A (KOSAN BIOSCIENCES INC ; ASHLEY GARY (US); FRYKMAN SCOTT (US); REGENTIN) 8 November 2001 (2001-11-08) page 87, paragraph 3 - page 88, paragraph 1 example 23	1-28

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/08483

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-28 (all in part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-28 (all in part)

Present claims 1-8 (effector conjugates) 9-11 (effector recognition unit conjugates) relate to an extremely large number of possible compounds. In fact, the claims contain so many options, variables, possible permutations and provisos that a lack of clarity (and conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. It appears however as there are no examples of effector conjugates and effector recognition unit conjugates in the description. Consequently, the search has been carried out for those conjugates where the effector element is one of the substances as listed in claim 3. The same limitation applieas analogously to method claims 19, 20, use claims 21-25 and first medical use claims 26-28.

Present product claims 12-18 (linkers) relate to an extremely large number of possible compounds. It is noted that for example the generic formula (III3) encompass trivial substances like carbon acid. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the linkers L1-L6a and L8-L18 in the description. Also with this limitation the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that only a fraction of the documents possibly relevant to novelty could be cited.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/08483

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/08483

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